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Original Article

Joint analysis of fasting and postprandial plasma glucose and insulin concentrations in Venezuelan women

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ABSTRACT

Aims: Plasma glucose and insulin concentrations in fasting and postprandial reflect the metabolism of glucose by the human body and are useful in the diagnosis of metabolic diseases, such as diabetes and insulin resistance. In this work, these concentrations are jointly analyzed in Venezuelan women and 28 classes that better specify each metabolic condition are generated.
Materials and methods: Each class comprises a combination of fasting and postprandial ranges of glucose and insulin concentrations defined in the literature as normal, impaired and diabetic. A hypothesis test was used to find statistically significant differences between the classes, and confidence intervals for age and glucose and insulin concentrations were defined for each class.
Results and conclusion: The process of deterioration of glucose metabolism advances with the age of the subject, more than half of the prediabetics have impaired glucose levels in fasting but normal in postprandial and normal insulin levels in fasting and postprandial, and one third of diabetics have diabetic glucose levels in fasting and postprandial and normal insulin levels in fasting and postprandial. This categorization of subjects would allow the application of a more specific treatment and the possibility of predicting the progress of the metabolic disorder.

1. Introduction

Functions of the human body are coordinated by the interaction of several chemical messaging systems: neurons release neurotransmitters in synaptic junctions and act locally to control the functions of nerve cells, and specialized glands or cells release endocrine hormones in circulating blood and they influence the functions of the cells in another location of the body. The endocrine hormones are transported by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many reactions [1]. β Cells and α cells, located in the pancreatic islets of Langerhans, secrete insulin and glucagon, respectively, to maintain glucose homeostasis [2]. Normal concentration of fasting blood glucose ranges 70–100 mg/dl [3]. When the level of blood glucose is higher than normal, the β cells secrete insulin, which is responsible for transporting glucose to the cells of the muscles or fats, thus lowering the blood glucose level. On the other hand, when the glucose level is lower than normal, the α cells secrete glucagon, this goes to the liver which releases glucose into the bloodstream thus increasing the blood glucose level. When this delicate balance is affected, metabolic diseases such as insulin resistance, obesity, and diabetes develop [4].

Insulin resistance is the decreased ability of cells to process insulin and thus promote the entry of glucose. The reasons why this disability occurs are unknown, and the drugs for its treatment are basically focused on improving the interaction between insulin and cells. Obesity is defined as an abnormal or excessive accumulation of fat that can detriment health. The body mass index (BMI) is the most used diagnostic tool for the characterization of obesity: BMI $\geq$ 25 implies overweight, BMI $\geq$ 30 implies obesity. Diabetes is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disorders of the metabolism of carbohydrates, fats, and proteins that are the result of defects in the secretion of insulin, the action of insulin or both [5]. Overweight and obesity are risk factors for numerous chronic diseases, including diabetes, cardiovascular diseases, and cancer [6]. Insulin resistance has been considered as prediabetic stage; the diagnosis and control of insulin

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resistance could prevent the development of diabetes [7]. Obesity and insulin resistance are related: people with high BMI are prone to develop insulin resistance [8].

Imbalances in glucose absorption can be studied by means of the oral glucose tolerance test (OGTT). This test involves the extraction of a blood sample after 8 h of fasting, then the patient ingests 75 g of pure glucose and, after 120 min, another blood sample is drawn. With the two blood samples, measurements of insulin and glucose concentrations are made in the laboratory. With the OGTT, glucose levels can be obtained in fasting (G_0, minute 0) and postprandial (G_{120}, 120 min after taking glucose). According to fasting and postprandial glucose levels, subjects can be classified as normal, prediabetic or diabetic [5,9]. In this sense, a normal subject has normal fasting glucose (NFG) and normal glucose tolerance (NGT). People with prediabetes have a blood glucose level higher than normal but not high enough as in the diabetic state. People with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are considered prediabetic. Finally, people with diabetes have diabetic fasting glucose (DFG) and/or diabetic glucose tolerance (DGT). Table 1 shows the reference range of glucose levels for each state and the respective conditions.

Similarly, insulin levels can also be determined with the OGTT in fasting (I_0, minute 0) and postprandial (I_{120}, 120 min after glucose intake). In this sense, subjects can have normal fasting insulin (NFI) or impaired fasting insulin (IFI), and normal postprandial insulin (NPI) or impaired postprandial insulin (IPI), as shown in Table 2 [10,11].

There is a directly proportional relationship between the development of IFG and IGT with obesity and the increase in insulin resistance [12]; It has been shown that the appearance of more than one of these factors increases the predisposition to develop diabetes by 20% [13]. It has also been indicated that the IGT that occurs concomitantly with NFG represents an intermediate metabolic state between normal and diabetic glucose homeostasis, that is, a prediabetic state [14]. It has been shown that 57% of subjects with IGT have obesity and insulin resistance [12,15,16].

Glucose values from the OGTT established in the literature are used for the diagnosis of IGT and IFG [17], however, among routine clinical examinations, only fasting glucose is prescribed. In low- and middle-income countries, this practice is very common because the OGTT is an expensive test, which leads to a delay in the diagnosis of IGT and, in many cases, that of diabetes manifested in the postprandial values [18]. To make an accurate diagnosis of prediabetes, both IGT and IFG should be taken into account since, for example, in 62 university women (19–23 years old) in Japan it was found that 7% presented IGT despite having normal fasting insulin and glucose patterns, which shows that baseline values could lead to false negatives [19]. In addition, the patterns of insulin concentration during the OGTT may be useful in the prediction of type 2 diabetes [20]. In this sense, Hayashi et al. noted that the incidence of type 2 diabetes in Japanese-American men during ten years of follow-up was 38%–48% in those who reached a maximum level of insulin at 120 min of the OGTT, and was significantly greater than those whose maximum levels of insulin occurred at 30 or 60 min (< 16%) [20].

According to the International Diabetes Federation, 415 million adults live with diabetes worldwide, almost half of whom are undiagnosed, and this number is expected to increase to 642 million by the year 2040. Like most noncommunicable diseases, three-quarters of those affected live in low- and middle-income countries [21]. In South America and Central America, 60% increase in the number of diabetic patients (from 24 to 38 million people) was estimated between 2013 and 2035 [22]. In 2013, the prevalence of diabetes in Colombia was between 7.1% and 8.5%, while it was 6.6% in Venezuela [22]. On the other hand, the prevalence of IFG in 2014 was 9.3% in men and 8.1% in women [23]. In Colombia, it was estimated that in 2018 at least 3.2 million adult patients have IFG or IGT, of which 66% were not diagnosed or treated and, therefore, are exposed to diabetes or cardiovascular events [24]. In Venezuela, the prevalence of IFG in 2008 in people older than 25 years was 11.1% in men and 10.9% in women [25]. The importance of identifying individuals with prediabetes lies in the possibility that their early management can stop the growing incidence of diabetes that is currently occurring, especially in low- and middle-income countries.

As it has been observed, few studies have jointly associated the conditions of glucose and insulin in fasting and postprandial for each state of the subject (normal, prediabetic, diabetic). The reason for this could be related to the discomfort of the subject for performing the OGTT (for example, fear of venipuncture), the time dedicated to performing the test, and the costs associated with an additional blood test. However, associating these conditions together could help in the understanding of the evolution of the metabolic disease, the consequent development of adequate and personalized treatment, avoid the advance of the condition and improve the quality of life of the patient. In addition, given the increasing technological progress experienced in the last decade, in particular in nanotechnology [26,27], contactless data acquisition [28,29] and wearable technology [30,31], and the growing need of the human beings to have control over their health (patient empowerment) [32] and to be constantly monitored through personal health records [33–35] and smartwatches [36–38], the obtaining of glucose and insulin values for different instants of time in a fast, reliable, non-invasive and intelligent way could be available in the near future.

The objective of this work is to jointly associate the conditions of insulin and glucose detailed in Tables 1 and 2 for each state of the subject in order to generate new classes that allow us to have a greater specificity of the state of the subject, and find the proportions in which the classes obtained are found in a sample population of 2835 Venezuelan women. Statistical analysis is carried out with the objective of finding significant differences between the age of the subjects and the glucose and insulin levels for each class.

2. Materials and methods

2.1. Classification of subjects according to the joint information of glucose and insulin levels

Using the information in Tables 1 and 2, the conditions of

Table 1
Classification of subjects based on fasting (G_0) and postprandial (G_{120}) glucose levels. The symbol $\wedge$ corresponds to the propositional logic of conjunction ("and") in which A $\wedge$ B is true if A and B are both true, while the symbol $\vee$ corresponds to the propositional logic of disjunction ("or") in which A $\vee$ B is true if A or B (or both) are true.

State	Condition	Glucose level (mg/dL)
Normal	NFG $\wedge$ NGT	$70 \leq G_0 < 100 \wedge 70 \leq G_{120} < 140$
Prediabetes	IFG $\vee$ IGT	$100 \leq G_0 < 126 \wedge 140 \leq G_{120} < 200$
Diabetes	DFG $\vee$ DGT	$126 \leq G_0 \vee 200 \leq G_{120}$

Table 2
Classification of subjects based on fasting (I_0) and postprandial (I_{120}) insulin levels.

Condition	Insulin level (μIU/mL)
NFI	$2 \leq I_0 < 25$
IFI	$25 \leq I_0$
NPI	$16 \leq I_{120} < 166$
IPI	$166 \leq I_{120}$

glucose and insulin can be combined with the states of the subjects (normal, prediabetes and diabetes) and thus generate new classes, as indicated in Table 3. This combination of conditions gives us a total of 28 different classes: 4 for the normal state, 12 for the prediabetic state and 12 for the diabetic state. In the table, in the diabetic state, we have considered that two conditions can be present (not simultaneously) to define the class, such is the case, for example, of class D1, corresponding to the condition (NFG ∨ IFG) ∧ DGT ∧ NFI ∧ NPI, where the subject can have, in addition to the last three conditions, normal or impaired fasting glucose.

2.2. Database

The subjects were included in the study if they met the following criteria, ages between 15 and 70 years, non-smoker, good general health (without evidence of physical disabilities or cardiovascular disease), do not take any medication. The exclusion criteria were: unable to meet the inclusion criteria, current alcohol or drug abuse.

In the morning, after a night of fasting, the 2-h two-sample OGTT was performed on the subjects. Plasma glucose and insulin levels were taken in fasting (G_0 and I_0) and 2 h after (postprandial) the oral intake of 75 g of liquid glucose (G_{120} and I_{120} at 120 min). The serum glucose concentrations were measured using the automated equipment of Hitachi® 902 while the insulin was determined by the IMMULITE 1000 immunoassay method of Siemens®.

The database was made up of 3254 subjects, of which 36 were men and 3218 were women. Given the imbalance in the number of male and female subjects, it was decided to do the study only in women. In addition, subjects with $G_0 < 70$ mg/dL or $G_{120} < 70$ mg/dL (below the normal range) and those with $I_{120} < 16$ μIU/mL (below the normal range) were eliminated. The resulting database consisted of 2835 subjects.

The clinical protocol was performed in the Clinical Research Laboratory of the Caracas University Hospital, Venezuela, between 2009 and 2013. All the procedures performed in the study were adjusted to the ethical standards of the University Hospital of Caracas and to the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards. The informed consent of all the participants included in the study was obtained.

2.3. Statistic analysis

The Kruskal-Wallis nonparametric statistical test was performed to find significant differences in the variables of interest (age, and fasting and postprandial glucose and insulin values) between the different classes (independent samples). In addition, Tukey's honestly significant difference test was used as post hoc test. A value of p less than or equal to 5% was considered statistically significant. Additionally, confidence intervals (CI) of 95% of age and glucose and insulin values were determined for each class and for each condition. Confidence intervals and statistical tests were performed only if the variables had at least ten samples.

3. Results

Tables 4 and 5 show the subjects' assignment according to the glucose and insulin values in fasting and postprandial, respectively, and the confidence intervals of age and glucose values for each condition. From these tables, it appears that most subjects have normal fasting (62.54%) and postprandial (82.65%) levels of glucose, and normal fasting (96.19%) and postprandial (94.85%) levels of insulin. It is also observed that subjects with normal fasting glucose are statistically significantly younger than subjects with impaired or diabetic glucose, and that subjects with impaired fasting glucose are statistically significantly younger than subjects with diabetic glucose. On the other hand, subjects with normal postprandial glucose are statistically significantly younger than subjects with impaired or diabetic glucose. No statistically significant differences were found in the age of the subjects for the different insulin conditions.

From the totality of subjects in the database (2835), 1654 (58.34%) were classified as normal, 969 (34.18%) as prediabetic and 212 (7.48%) as diabetic. Table 6 shows the classification of normal subjects according to the proposed classes. From this table it is observed that class N1 (subjects with normal glucose and insulin levels in fasting and postprandial) represents the most representative sample (94.86%) while class N4 (subjects with normal fasting and postprandial glucose levels, but with impaired fasting and

Table 3
Classification of subjects based on fasting (G_0, I_0) and postprandial glucose and insulin levels (G_{120}, I_{120}). The symbol ∧ corresponds to the propositional logic of conjunction ("and") in which A ∧ B is true if A and B are both true, while the symbol ∨ corresponds to the propositional logic of disjunction ("or") in the which A ∨ B is true if A or B (or both) are true.

State	Condition	Class
Normal	NFG ∧ NGT ∧ NFI ∧ NPI	N1
	NFG ∧ NGT ∧ NFI ∧ IPI	N2
	NFG ∧ NGT ∧ IFI ∧ NPI	N3
	NFG ∧ NGT ∧ IFI ∧ IPI	N4
Prediabetic	NFG ∧ IGT ∧ NFI ∧ NPI	P1
	NFG ∧ IGT ∧ NFI ∧ IPI	P2
	NFG ∧ IGT ∧ IFI ∧ NPI	P3
	NFG ∧ IGT ∧ IFI ∧ IPI	P4
	IFG ∧ NGT ∧ NFI ∧ NPI	P5
	IFG ∧ NGT ∧ NFI ∧ IPI	P6
	IFG ∧ NGT ∧ IFI ∧ NPI	P7
	IFG ∧ NGT ∧ IFI ∧ IPI	P8
	IFG ∧ IGT ∧ NFI ∧ NPI	P9
	IFG ∧ IGT ∧ NFI ∧ IPI	P10
	IFG ∧ IGT ∧ IFI ∧ NPI	P11
	IFG ∧ IGT ∧ IFI ∧ IPI	P12
Diabetic	(NFG ∨ IFG) ∧ DGT ∧ NFI ∧ NPI	D1
	(NFG ∨ IFG) ∧ DGT ∧ NFI ∧ IPI	D2
	(NFG ∨ IFG) ∧ DGT ∧ IFI ∧ NPI	D3
	(NFG ∨ IFG) ∧ DGT ∧ IFI ∧ IPI	D4
	DFG ∧ (NGT ∨ IGT) ∧ NFI ∧ NPI	D5
	DFG ∧ (NGT ∨ IGT) ∧ NFI ∧ IPI	D6
	DFG ∧ (NGT ∨ IGT) ∧ IFI ∧ NPI	D7
	DFG ∧ (NGT ∨ IGT) ∧ IFI ∧ IPI	D8
	DFG ∧ DGT ∧ NFI ∧ NPI	D9
	DFG ∧ DGT ∧ NFI ∧ IPI	D10
	DFG ∧ DGT ∧ IFI ∧ NPI	D11
	DFG ∧ DGT ∧ IFI ∧ IPI	D12

Table 4
Assignment of subjects to fasting and postprandial glucose conditions.

Time	Condition	# subjects	CI age[a,b,c,d,e]	CI glucose[a,b,c,d,e,f]
Fasting	NFG	1773 (62.54%)	[38.08, 9.41]	[89.09, 89.68]
	IFG	891 (31.43%)	[47.38, 49.19]	[107.04, 107.87]
	DFG	171 (6.03%)	[50.91, 54.21]	[149.03, 163.25]
	Total	2835 (100%)		
Postprandial	NGT	2343 (82.65%)	[40.29, 41.49]	[104.16, 105.50]
	IGT	363 (12.80%)	[48.41, 51.09]	[158.93, 162.39]
	DGT	129 (4.55%)	[51.16, 54.82]	[257.07, 280.56]
	Total	2835 (100%)		

[a] Significant difference between NFG and IFG.
[b] Significant difference between NFG and DFG.
[c] Significant difference between IFG and DFG.
[d] Significant difference between NGT and IGT.
[e] Significant difference between NGT and DGT.
[f] Significant difference between IGT and DGT.

Table 5
Assignment of subjects to fasting and postprandial insulin conditions.

Time	Condition	# subjects	CI age	CI insulin[a,b]
Fasting	NFI	2727 (96.19%)	[42.01, 43.12]	[7.64, 8.04]]
	IFI	108 (3.81%)	[39.98, 45.89]	[31.92, 35.58
	Total	2835 (100%)		
Postprandial	NPI	2689 (94.85%)	[41.97, 43.09]	[56.06, 58.56]
	IPI	146 (5.15%)	[40.81, 45.90]	[207.16, 218.17]
	Total	2835 (100%)		

[a] Significant difference between NFI and IFI.
[b] Significant difference between NPI and IPI.

postprandial insulin levels) represents the least representative sample (0.67%). This means that subjects who have normal glucose and insulin levels in both fasting and postprandial usually have normal insulin values in both fasting and postprandial. It can also be highlighted that subjects with normal fasting insulin but impaired postprandial insulin have higher levels of postprandial glucose and higher fasting and postprandial insulin levels than those with normal fasting and postprandial insulin.

Table 7 shows the classification of prediabetic subjects according to the proposed classes. From this table it is observed that class P5 (subjects with impaired fasting glucose but normal in postprandial and normal insulin levels in fasting and postprandial) represents the most representative sample (63.47%) while class P3 (subjects with normal fasting glucose but impaired in postprandial and impaired fasting insulin but normal in postprandial) represents the least representative sample (0.10%). This means that subjects who have impaired fasting glucose values do not necessarily have impaired postprandial glucose and have normal fasting and postprandial insulin levels. It can also be noted that subjects with normal insulin values in fasting and postprandial but impaired glucose in fasting (P5) or postprandial (P1) are significantly younger than those who have both impaired fasting and postprandial glucose levels (P9), which suggests that the prevalence of IGT and IFG increase with age. On the other hand, compared to class P5, class P9 has higher levels of fasting and postprandial glucose and higher levels of postprandial insulin.

Table 8 shows the classification of diabetic subjects according to the proposed classes. From this table it is observed that classes D9 (subjects with diabetic glucose levels in fasting and postprandial and normal insulin levels in fasting and postprandial) and D5 (subjects with diabetic glucose levels in fasting and diabetic levels or impaired in postprandial and normal insulin levels in fasting and postprandial) represent the most representative samples (34.91% and 33.49%, respectively) while class D12 (subjects with diabetic glucose levels in fasting and postprandial and normal insulin levels in fasting and postprandial) represents the least representative sample (0.10%). This means that subjects who have diabetic glucose levels in fasting and diabetic or impaired glucose in postprandial have normal insulin levels in fasting and postprandial. Class D9 has higher fasting and postprandial glucose levels than classes D1 and D5. No significant differences were found in age or insulin levels between classes.

4. Discussion

In this work, we have been shown that women with NGT are younger than those with IFG and IGT (see Table 4), which is consistent with similar studies, suggesting that as we older increases the prevalence of IGT, IFG, DGT and DFG [39,40]. In addition, it was found that women with IFG are younger than those with DFG. These results show that the natural evolution of the metabolic disease goes from normal values in fasting to abnormal values in fasting and then to diabetes. The fact that there were no significant differences in age between IGT and DGT could indicate that both conditions occur in the same age range. Similarly, the fact that there were no significant differences in age between the different insulin conditions (see Table 4) could indicate that the prevalence of suffering IFI and IPI is independent of age.

In Table 6, it was shown that classes N2 and N4 are those that produce higher amounts of postprandial insulin, but they are also the groups that present the highest amounts of fasting and postprandial glucose. Similar results were obtained in Refs. [41,42], from which it follows that producing large amounts of insulin does not guarantee an efficient metabolization of glucose, unlike what happens in athletes who, with minimal quantities of insulin, achieve efficient homeostasis of glucose [43].

The significant differences in fasting insulin levels between the groups N1 and N2, P1 and P2, and P9 and P10, reported in Tables 6 and 7, could suggest that fasting insulin concentration could discriminate between subjects who have IPI of those that do not, as suggested in Ref. [44]. Furthermore, even though fasting insulin confidence intervals are within the normal range, they are statistically different between groups (N1 vs N2: 6.67–7.15 vs 13.60–17.16, P1 vs P2: 5.78–7.73 vs 10.36–15.52, P9 vs P10: 7.19–8.60 vs 12.19–15.92). In addition, given that the fasting insulin level between the groups P2 [10.36–15.52] and P10 [12.19–15.92] did not show significant differences between them, a range of fasting insulin could be established where there are high probabilities of presenting IPI, taking the minimum and maximum values between the confidence intervals of groups P2 and P10. In this sense, it could be said that those subjects with IGT who show fasting insulin level between 10.36 and 15.92 μIU/mL, have a high probability of presenting IPI.

Although there were no statistically significant differences in fasting and postprandial insulin levels between the diabetic classes (see Table 8), these subjects have very high blood glucose levels and do not produce the insulin needed to maintain the glucose homeostasis. Subjects with DGT and DFG (class D9) have the highest values of fasting and postprandial glucose, similar to what was found in fasting glucose levels of classes P1, P5 and P9, where class

Table 6
Assignment of subjects to the normal class. The percentage of each class was taken from the total number of subjects in the database classified as normal (1654 subjects).

Class	# subjects	CI age	CI glucose		CI insulin	
			Fasting[b]	Postp[a,d]	Fasting[a,b,c]	Postp[a,b,c,d]
N1	1569 (94.86%)	[37.71, 39.12]	[88.80, 89.42]	[100.46, 102.03]	[6.67, 7.15]	[51.53, 54.58]
N2	41 (2.48%)	[30.20, 39.99]	[88.70, 93.30]	[112.34, 122.34]	[13.60, 17.16]	[205.55, 227.47]
N3	33 (2.00%)	[37.06, 48.99]	[90.17, 94.25]	[95.39, 107.76]	[29.93, 37.18]	[76.94, 103.05]
N4	11 (0.67)	[21.22, 37.13]	[84.41, 94.86]	[102.05, 122.50]	[28.78, 34.51]	[183.33, 235.40]

[a] Significant difference between N1 and N2.
[b] Significant difference between N1 and N3.
[c] Significant difference between N1 and N4.
[d] Significant difference between N2 and N3.

Table 7
Assignment of subjects to the prediabetes class. The percentage of each class was taken from the total number of subjects in the database classified as prediabetic (969 subjects).

Class	# subjects	CI age[e,h,j,n,p]	CI glucose		CI insulin	
			Fasting[b,c,d,e,f,g,h,i,j,k,n]	Postp[b,c,d,g,h,i,n,o,p,q,r,s]	Fasting[a,c,d,f,g,j,m,o,r,s,t]	Postp[a,b,c,f,g,i,j,l,m,n,o,p,s,t]
P1	91 (9.39%)	[40.84, 46.37]	[90.34, 92.85]	[154.68, 161.08]	[5.78, 7.73]	[75.48, 91.62]
P2	17 (1.75%)	[34.94, 44.24]	[89.93, 94.42]	[153.11, 167.48]	[10.36, 15.52]	[201.55, 232.56]
P3	1 (0.10%)	N/A	N/A	N/A	N/A	N/A
P4	3 (0.31%)	N/A	N/A	N/A	N/A	N/A
P5	615 (63.47%)	[45.73, 47.92]	[105.88, 106.77]	[110.41, 112.80]	[8.01, 8.84]	[51.07, 55.64]
P6	14 (1.44%)	[47.91, 62.38]	[102.79, 108.92]	[115.35, 129.08]	[9.69, 16.41]	[182.78, 209.08]
P7	24 (2.48%)	[35.09, 47.91]	[107.11, 113.47]	[101.31, 117.44]	[29.75, 39.87]	[71.88, 104.53]
P8	7 (0.72%)	N/A	N/A	N/A	N/A	N/A
P9	165 (17.03%)	[51.44, 55.13]	[108.89, 111.05]	[156.75, 161.76]	[7.19, 8.60]	[72.15, 83.41]
P10	24 (2.48%)	[45.03, 54.97]	[105.63, 110.78]	[151.33, 163.75]	[12.19, 15.92]	[191.08, 215.25]
P11	3 (0.31%)	N/A	N/A	N/A	N/A	N/A
P12	5 (0.52%)	N/A	N/A	N/A	N/A	N/A

[a] Significant difference between P1 and P2.
[b] Significant difference between P1 and P5.
[c] Significant difference between P1 and P6.
[d] Significant difference between P1 and P7.
[e] Significant difference between P1 and P9.
[f] Significant difference between P1 and P10.
[g] Significant difference between P2 and P5.
[h] Significant difference between P2 and P6.
[i] Significant difference between P2 and P7.
[j] Significant difference between P2 and P9.
[k] Significant difference between P2 and P10.
[l] Significant difference between P5 and P6.
[m] Significant difference between P5 and P7.
[n] Significant difference between P5 and P9.
[o] Significant difference between P5 and P10.
[p] Significant difference between P6 and P9.
[q] Significant difference between P6 and P10.
[r] Significant difference between P7 and P9.
[s] Significant difference between P7 and P10.
[t] Significant difference between P9 and P10.

Table 8
Assignment of subjects to the diabetes class. The percentage of each class was taken from the total number of subjects in the database classified as diabetic (212 subjects).

Class	# subjects	CI age	CI glucose		CI insulin	
			Fasting[a,b,c]	Postp[a,c]	Fasting	Postp
D1	29 (13.68%)	[49.49, 56.65]	[105.28, 113.89]	[226.05, 259.06]	[7.29, 11.47]	[64.85, 93.08]
D2	6 (2.83%)	N/A	N/A	N/A	N/A	N/A
D3	2 (0.94)	N/A	N/A	N/A	N/A	N/A
D4	4 (1.89)	N/A	N/A	N/A	N/A	N/A
D5	71 (33.49)	[49.70, 55.26]	[135.09, 142.82]	[146.33, 160.21]	[8.27, 11.04]	[49.13, 66.58]
D6	6 (2.83)	N/A	N/A	N/A	N/A	N/A
D7	4 (1.89)	N/A	N/A	N/A	N/A	N/A
D8	2 (0.94)	N/A	N/A	N/A	N/A	N/A
D9	74 (34.91)	[51.47, 56.12]	[159.42, 182.56]	[265.93, 297.72]	[9.63, 12.66]	[52.93, 69.14]
D10	5 (2.36)	N/A	N/A	N/A	N/A	N/A
D11	8 (3.77)	N/A	N/A	N/A	N/A	N/A
D12	1 (0.47)	N/A	N/A	N/A	N/A	N/A

[a] Significant difference between D1 and D5.
[b] Significant difference between D1 and D9.
[c] Significant difference between D5 and D9.

P9 (subjects with IGT and IFG) presents the highest glucose levels compared to P1 (subjects with IGT) and P5 (subjects with IFG). This confirms the fact that when two of the conditions occur in concomitance, the metabolic disorder worsens [45].

The importance of this study lies in the joint analysis of the combination of conditions associated with fasting and postprandial glucose and insulin levels in normal, prediabetic and diabetic subjects. However, there were some practical difficulties and limitations that should be highlighted. One of the challenges was the recruitment of subjects since the financial restrictions and the willingness of the subjects to perform the OGTT test led to few diabetic subjects performing the clinical protocol (almost 10% of normal subjects). In addition, the low commitment and willingness of male subjects to perform the test led to this work being done only in women. Another limitation was that subjects with hypoglycemia were not included. A later study could include this population and thus analyze the combinations of glucose and insulin in this group. Our research team is currently working on conducting an exploratory analysis using clustering techniques such as k-means in order to observe if the association of subjects responds to the classes generated from the values used in clinical practice as well as the disclosure of unknown subgroups even unrelated to classes, as was recently done in Ref. [46].

5. Conclusions

The results of this work showed that, by combining the glucose and insulin ranges of the OGTT defined in the literature in normal, prediabetic and diabetic subjects, it was possible to generate new classes (4 normals, 12 prediabetics, and 12 diabetics) that are more specific to the conditions of the subjects. This specificity allowed a more detailed exploration of the demographic and biochemical characteristics in each created class. In addition, the statistical analysis allowed highlighting statistically significant differences between the classes created, and the confidence intervals allowed to define the ranges in which the subjects' age and the glucose and insulin levels for each class are concentrated. One of the main implications of these results is the possibility of analyzing the progress of the deterioration of the glucose metabolism process until the appearance of diabetes from the classes created, that is, observing the sequence of most probable classes when passing from a normal class to a prediabetic and then to a diabetic class. Our research team is currently working in this direction. By fully understanding the progress of the disease, early diagnosis of metabolic diseases could be made or a more appropriate treatment could be applied.

Conflicts of interest

The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.05.029.

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