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Strategy to establish a cut-off point for hyperinsulinemia

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The Fasting Plasma Insulin (FPI) is often used in clinical medicine to classify subjects in a binary categorization of normal versus hyperinsulinemic patients. The cut-off point for hyperinsulinemia in the literature is variable and has led to the proposal that each laboratory should establish its own cut-off point.[1] or as proposed by WHO, to use an arbitrary percentile value of the FPI distribution as a cut-off point.[2]

We offer here a strategy that could prove useful to others, to establish hyperinsulinemia in a population group.

To illustrate the procedure we shall use insulin values seen in 443 adults (253 women, 190 men) living in the Mexican State of Yucatan. Some subjects (N = 183) were urbanites living in the State Capital of Merida, and others (N = 260) were rural subjects living in two small communities (Uci and San Rafael with populations < 12 hundred). Blood pressure, height and weight, and circumferences of waist and hip were measured at the time of blood sampling. The blood was collected in vaccum tubes containing sodium fluoride to prevent glycolisis, and stored on ice during its transportation to the laboratory of the Hospital O'Horan in Merida run by personnel of the University of Yucatan. The urban samples were delivered to the laboratory 1-3 hours after sampling whereas the rural ones took 3-5 hours. Upon arrival, plasma was separated, refrigerated, and the biochemical assays (FPI = fasting plasma insulin, FPG = fasting plasma glucose, cholesterol, triglycerides, LDL and HDL) were performed on the following day in an automated analyzer (Boehringer Mannheim, Germany). Two indices (BMI = body mass index and WHR = waist to hip ratio) were calculated with the anthropometric data. The personnel that measured blood pressure and anthropometry had been trained and standardized by us prior to the start of the study. The Ethics Committe of the O'Horan Hospital approved the study and written consent was obtained from the urban subjects and from the municipal authorities of the rural communities.

Intergroup differences were evaluated with the Student t test and confirmed by the Mann-Whitney test. Logistic regression analysis were performed using SPSS 15.0.

Insulin and triglycerides had the highest variability in the 443 samples (CVs of 65 and 64 respectively), whereas the other 12 variables had CVs of 9 to 37. The median insulin was 18 µU/mL and ranged from 2 to 80.

We performed four forward step-wise logistic regressions using age, gender and 13 anthropometric and laboratory variables, as potential predictors for hyperinsulinemia. We varied the cut-off point for hyperinsulinemia in each regression (> 15, > 20, > 25, ≥ 30 µU/mL). The four regressions showed BMI and glucose as the only significant predictors. On this basis, we formed 12 groups by crossing four categories of fasting glucose level with three of BMI. The descriptive statistics for insulin in the 12 groups are shown in Table 1. The mean insulin of Group 1 (non-diabetics with no overweight) was compared with that of the other 11 groups. With the exception of Group 4 (glucose 100-109 mg/dL with no overweight), the other 10 groups had a significantly higher mean insulin than Group 1 (Table 1). On the basis of the non significant FPI difference between groups 1 and 4, we proceeded to pool them into a single group of 91 subjects characterized by a glucose < 110 mg/dL and BMI < 25 kg/m^2.

Table 1. Group differences of mean insulin level in 12 groups. Cross of four categories of Fasting Plasma Glucose (FPG) and three of Body Mass Index (BMI).

Group	FPG (mg/dL)	BMI (kg/m^2)	INSULIN N	INSULIN Mean	INSULIN SD	Difference *vs* Group 1
1	< 100	< 25	75	13.7	6.1	-
2		25-29	120	16.6	7.7	0.007
3		30+	81	23.7	10.5	<0.0005
4	100-109	< 25	16	12.3	3.6	0.39 NS
5		25-29	31	17.4	6.6	0.006
6		30+	41	28.1	10.1	< 0.0005
7	110-125	< 25	5	22.1	7.5	0.004
8		25-29	9	22.4	11.1	0.048
9		30+	14	29.8	14.7	0.001
10	> 125	<25	5	25.7	16.7	< 0.0005
11		25-29	26	23.0	12.8	0.001
12		30+	20	37.6	19.3	< 0.0005
	GLOBAL		443	20.6	13.3	-

In the pooled group, we identified four extreme values in the insulin distribution (27 to 36 µU/mL) using the SPSS Explore procedure that considers as extreme values those surpassing the value given by P75 (percentile 75) + 1.5 times the interquartilar distance (or below P25 minus the same distance). These four values were eliminated and in the remaining 87 cases, the mean FPI (in µU/mL) was 12.6 ± 4.3 (SD) and the median was 12 and ranged from 5 to 23.

Our strategy involved five steps that can se summarized as follows:

- ***Step 1.*** We identified predictor variables for hyperinsulinemia using step-wise logistic regressions with four cut-off points of insulin (15, 20, 25 and 30 µU/mL).
  - Only BMI (Body Mass Index) and FPG (Fasting Plasma Glucose) appeared as predictors of hyperinsulinemia in the four regressions.

- ***Step 2.*** We thus formed 12 groups of subjects by crossing four categories of FPG with three of BMI and compared the mean of plasma insulin of Group 1 (G1) versus the other 11 groups.
  - Only G4 did not differ significantly from G1.

- ***Step 3.*** We pooled the subjects of G1 and G4 (N = 91) and explored for the presence of extreme values of FPI in the pooled group.
  - Four extreme values were present in G1, and none in G4.
  - It should be noted that the lack of extreme values in G4 and its non-significant difference *vs.* G1 goes against the concept that a glucose of 100-109 mg/dL indicates an abnormal carbohydrate metabolism.

- ***Step 4.*** We eliminated the extreme values to obtain a Reference Group (N = 87).
- ***Step 5.*** We obtained the descriptive statistics of the Reference Group.
  - We opted for the maximum value of the Reference Group as the cut-off point.

A cut-off point of > 23 µU/mL is similar to the P75 value of 22.5 used by a group of Mexican researchers to classify hyperinsulinemia.[3] On the other hand it is higher than other proposals, ie. 17 µU/mL by Bakerman.[4] We believe our approach is less arbitrary than the use of a percentile value to classify hyperinsulinemia as proposed by WHO. With a percentilar value one is deciding a priori that a certain proportion of the population is hyperinsulinemic which may not always be the case, ie. in our study, 69.5% of the population was below 23 uU/mL and our P75 was 25 uU/mL. This means that 5.5% of our presumably hyperinsulinemic subjects would be classified as normal if the P75 cut-off point is used.

In conclusion, we have decided to classify our Yucatan cases as hyperinsulinemics if the FPI is above 23 µU/mL. On the other hand, we do not think the

23 cut-off point will be the same in other populations due, among many factors, to differing methodologies. The approach described here would have to be applied in every new population study to overcome potential methodologic differences.

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