



Bimodal blood glucose distribution in a Mexican Indian population. Should diagnostic cutoff values be revised in specific populations?

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Abstract

Background: Bimodal distribution of glucose concentrations may be a universal phenomenon, but its use in establishing diagnostic cut off values is limited. The purpose of this study was to evaluate the presence of bimodality in the distribution of fasting and two-hour post-load glucose-values, and the cutoff point that best identifies subjects with diabetes in an indigenous population.

Methods: Mexican Indians ≥ 35 years old were invited to participate in a cross-sectional study, 394 Zapotec and 730 Mixe Indians were included. A normal distribution and a mixture of two normal distributions were fitted to fasting and two-hour post-load glucose-values. To assess the presence of bimodality, the mixture model was compared to the unimodal and the cutoff value for normal glycemia was calculated as the crossing point of the two normal distributions in the mixture model.

Results: Bimodal distribution was observed in the oral glucose tolerance test and the chi-square likelihood ratio statistic showed differences between the unimodal and the normal bimodal models. The cutoff value for diagnosing diabetes with fasting glucose was 6.41 mmol/l, whereas it was 7.96 mmol/l for the two-hour post-load glucose.

Conclusions: In these Mexican Indians, the fasting and the 2-hour post-load glucose values show bimodal distribution. The cutoff points for diagnosing diabetes are set below the current ones as seen in other populations where the diabetes epidemic is evolving.

Keywords: Bimodality, glucose tolerance test, diabetes mellitus, type 2, prediabetic state, Mexican Indians

Introduction

While it has recently been suggested that the bimodal distribution of glucose concentrations in blood is a universal phenomenon, it has not been necessarily used in establishing glucose cutoff points for diagnosing diabetes [1,2].

Diabetes is diagnosed based on glucose levels, either a fasting glucose ≥ 126 mg/dL (7.0 mmol/l) or a value ≥ 200 mg/dL (11.0 mmol/l) two hours after administering a glucose load containing the equivalent of 75g of anhydrous glucose dissolved in water and administered orally [3]. Another proposal is that a $\geq 6.5\%$ level of glucosylated hemoglobin allows for a diagnosis of diabetes [4], although recent studies have shown a lack of sensitivity with this test [5]. Regardless of the parameter employed, what holds true is that a variable with continuous distribution can be dichotomized to establish a diagnosis and the cutoff point will be arbitrary, though the result of consensus.

The term pre-diabetes, used with growing frequency, includes two main categories: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Both conditions take into account the presence of glucose values higher than those established as normal (either two hours post-

load ≥ 140 mg/dL or 7.8 mmol/l for IGT, or fasting glucose ≥ 100 mg/dL or 5.6 mmol/l for IFG) though lower than those used to diagnose diabetes. While these conditions imply early stages or stages prior to the onset of the disease, they also bespeak our inability to appropriately determine the presence of disease based on the distribution of a continuous variable. For example, the prevalence of diabetic retinopathy progressively increases with rising glucose or glucosylated hemoglobin values, even before the cutoff points used to diagnose diabetes [6,7], which in turn implies that some subjects classified as pre-diabetic in fact already have the disease. At the same time, the United Kingdom Prospective Diabetes Study (UKPDS) documented subjects with low glucose levels at the time of diabetes diagnosis; these were at lower risk of presenting complications or deaths linked to diabetes [8]. While it has been proposed that these subjects may represent population exhibiting diabetes identified at an earlier stage of the disease or presenting a different form of the disease that is less susceptible to complications [8], they could, in fact, also correspond to the upper end of the normal distribution curve of subjects

without diabetes.

A bimodal distribution implies the presence of two normal distribution curves: that of subjects with diabetes and that of subjects without diabetes. Given that the curves overlap, it is difficult to establish an appropriate cutoff point. While it is true that a determined cutoff point is necessary in order to establish uniform diabetes diagnosis criteria, it is important to study different populations in order to estimate the cutoff point that better differentiates the two distribution curves in a particular population.

The purpose of this study is to evaluate the presence of bimodality in the distribution of fasting blood glucose values and two-hour post-load glucose values, as well as the cutoff point that better identifies diabetic subjects in an indigenous population of Mexico in which the diabetes epidemic is in full progress. A bimodal fasting glucose distribution was observed in this populations and cut off values were identified for diagnosing diabetes.

Methods

Background and subjects

This study is part of a research project on diabetes and alterations in glucose metabolism in an indigenous population comprising Zapotec and Mixe individuals from the state of Oaxaca in Mexico; the results of the occurrence of diabetes and other alterations in glucose metabolism have already been published [9].

The state of Oaxaca lies in the south of the country and has the highest population of Mexican Indians. There are various types of ethnic groups in Oaxaca, with Zapotec and Mixe being the largest groups. Medical service for the population lacking in social security services in the rural zone of the state of Oaxaca is provided through the IMSS-Oportunidades program, a health program provided by the Federal Government and serviced by the Mexican Social Security Institution (IMSS). Healthcare for this population is offered in two manners: medical care and community care, both focusing on primary healthcare. There are 470 rural medical units in the state (first level healthcare), assigned to 9 rural hospitals (second level healthcare).

The rural hospital of Tlacolula was chosen as the study site; this community is located in the Central Valley region, 38 kilometers from the state capital, the city of Oaxaca. During a second phase, five communities in the zone handled by the Tlacolula hospital were selected. Two communities of Zapotec population were included: Santa María Albarradas (336 inhabitants ≥ 35 years of age) and San Juan del Río (698 inhabitants ≥ 35 years of age) and three communities of Mixe population: San Pedro and San Pablo Ayutla (829 inhabitants ≥ 35 years of age), Santa María Tepantlali (853 inhabitants ≥ 35 years of age) and Asunción Cacalotepec (438 inhabitants ≥ 35 years of age). Community authorities assisted in eliciting the participation of Mexican Indians 35 years of age or more. Since not all inhabitants were Mexican Indians, participation fluctuated

at around 20.5% of the total population in Ayutla to 58.4% in Cacalotepec.

The criteria for selection of participants was that they had to have been born in the community, that they speak Zapotec or Mixe (according to community of residence), or, in case they did not speak their native tongue, that both parents speak it. Where this was not the case, they were considered to be mestizos (mixed race) and were excluded from the study.

Survey procedures

All subjects were asked to report to the local rural medical unit where they were interviewed, and anthropometric measurements and blood glucose levels were taken.

An oral glucose tolerance test (OGTT) was used to diagnose alterations in glucose metabolism. Following overnight fasting of 10 to 12 hours, 75g. of glucose was administered orally. Concentrations of fasting glucose were measured, as well as at 30, 60 and 120 minutes after administering the oral glucose load. Glucose values were measured in the field using a glucose analyzer (Beckman Instruments Co., Fullerton, CA). The World Health Organization (WHO) classification was used to classify abnormalities in glucose metabolism [10]. In short, impaired fasting glucose was considered to be glucose values ranging from 6.1 to 6.9 mmol/l (110 to 125 mg/dL) and at 2 hours, lower than 7.8 mmol/l (140 mg/dL). Impaired glucose tolerance was determined when fasting values were lower than 7.0 mmol/l (126 mg/dL) and at 2 hours were equal to or greater than 7.8 and lower than 11.0 mmol/l (140 and 200 mg/dL). Diabetes was diagnosed when the fasting values were equal to or greater than 7.0 mmol/l (126 mg/dL) or at 2 hours were equal to or greater than 11.0 mmol/l (200 mg/dL). Subjects who had been given a prior diabetes diagnosis or who had taken insulin or any hypoglycemic medication were also considered to have diabetes, independently of the fasting glucose values or 2 hour post-load values.

All subjects participating in the study gave informed consent and all procedures were done in accordance with the principles of the Declaration of Helsinki as revised in 2000. The National Commission of Scientific Research at IMSS (Comisión Nacional de Investigación Científica) approved the research protocol. The authors declare that they have no conflict of interest.

Statistical analysis

A normal distribution and a mixture of two normal distributions were fitted to the glucose data. All subjects were included in the analysis, except those with a previous diagnosis of diabetes. We fitted the normal distribution using the maximum likelihood method, while the mixture model was fitted using a combination of a Newton-type method and the expectation-maximization (EM) algorithm (the normal mixEM2comp function from the Mixtools

Table 1. Prevalence of glucose metabolism abnormalities, according to demographic characteristics of the studied population.

Variable	Normal n(%)	IFG n(%)	IGT n(%)	Diabetes n(%)	Total
Town					
Santa María Albarradas	146 (85.4)	9 (5.3)	9 (5.3)	7 (4.1)	171
Ayutla	124 (72.9)	7 (4.1)	18 (10.6)	21 (12.4)	170
San Juan del Río	150 (67.3)	14 (6.3)	23 (10.3)	36 (16.1)	223
Tepantlali	250 (82.0)	15 (4.9)	27 (8.9)	13 (4.3)	305
Cacalotepec	220 (86.3)	6 (2.4)	14 (5.5)	15 (5.9)	255
Ethnic Group					
Zapoteco	296 (75.1)	23 (5.8)	32 (8.1)	43 (10.9)	394
Mixe	594 (81.4)	28 (3.8)	59 (8.1)	49 (6.7)	730
Sex					
Male	265 (82.0)	21 (6.5)	18 (5.6)	19 (5.9)	323
Female	625 (78.0)	30 (3.7)	73 (9.1)	73 (9.1)	801
Age Group (yrs)					
35 – 44	342 (83.2)	15 (3.6)	19 (4.6)	35 (8.5)	411
45 – 54	256 (78.0)	19 (5.8)	32 (9.8)	21 (6.4)	328
55 – 64	170 (75.2)	13 (5.8)	22 (9.7)	21 (9.3)	226
≥ 65	122 (76.7)	4 (2.5)	18 (11.3)	15 (9.4)	159
Total	890 (79.2)	51 (4.54)	91 (8.10)	92 (8.19)	1124
	-	3.4 – 5.9*	6.6 – 9.8*	6.7 – 9.9*	-

*95% confidence intervals.

package in R).

To assess the presence of bimodality, the mixture model was compared with the unimodal distribution using the likelihood ratio test and p-values for significance of the mixed model were based on a chi-square distribution with 4 degrees of freedom [11]. A cutoff point for normal glycemia was calculated as the crossing point of the two normal distributions in the mixture model. Approximate 95% confidence intervals (CI) for the cutoff points were estimated by bootstrapping 1,000 samples [12] using empirical percentiles.

Results

The study encompassed 1,124 subjects, with a greater proportion of women (71.3%) than men (28.7%). The prevalence of diabetes was 8.19% (95% confidence intervals 6.7–9.9%) and the age-adjusted prevalence was 8.27%, using the WHO reference population age structure. (Table 1) shows the target population’s demographic characteristics. The prevalence of diabetes was higher in the Zapotec population, in women, and there were no significant differences in the prevalence of diabetes per age group.

Bimodal distribution was observed in the oral glucose tolerance test (basal, 30, 60 and 120 minutes), and for all of these the chi-square likelihood ratio statistic showed a significant difference between the unimodal model and the normal bimodal model ($p < 0.0001$).

(Figure 1) shows the distribution model and the underlying curves for impaired fasting glucose values. While there are clearly two differentiated modes for the distribution of values, it is also evident that the extreme values of both

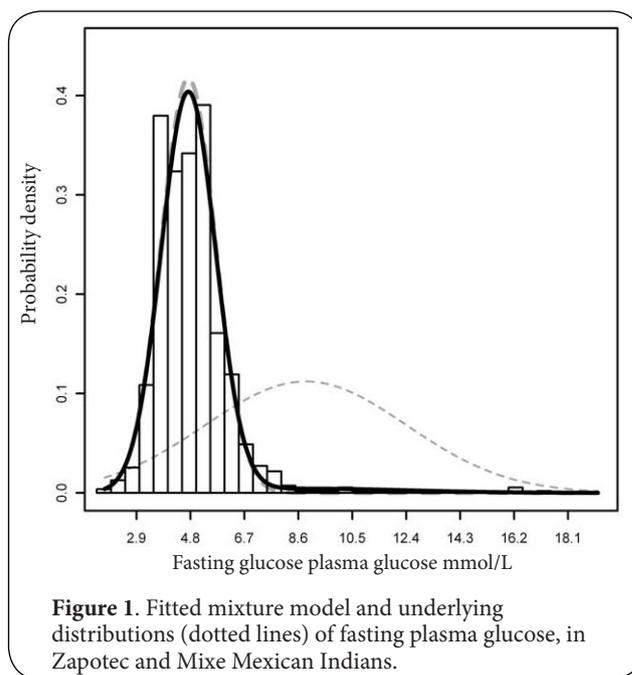


Figure 1. Fitted mixture model and underlying distributions (dotted lines) of fasting plasma glucose, in Zapotec and Mixe Mexican Indians.

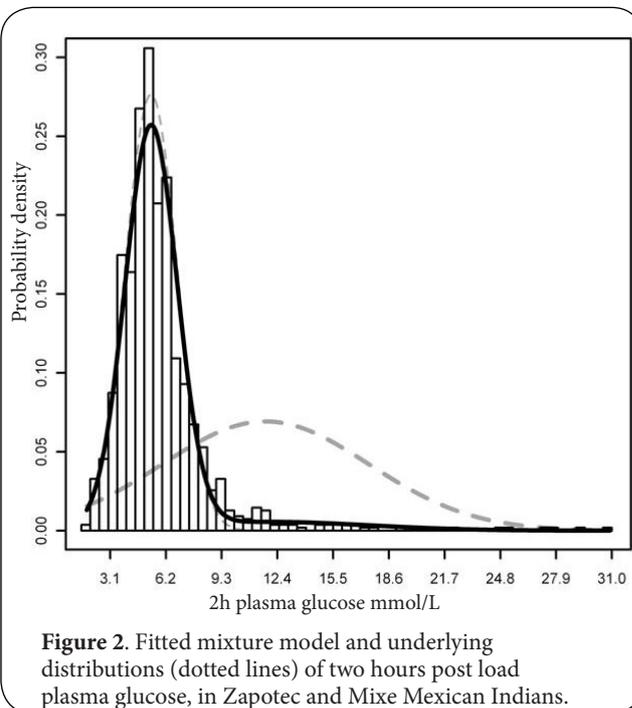


Figure 2. Fitted mixture model and underlying distributions (dotted lines) of two hours post load plasma glucose, in Zapotec and Mixe Mexican Indians.

distribution curves are superimposed. (Figure 2) denotes a similar situation for blood glucose values two hours after the administration of an oral glucose load.

The cutoff point for fasting glucose that better differentiated the normal curve of subjects without diabetes from those with diabetes was 115 mg/dL (6.41 mmol/L), whereas two-hour post-load glucose was registered at 143 mg/dL (7.96 mmol/L), as seen in (Table 2).

Table 2. Mean and standard deviation of both glucose distribution curves and cut off point values with 95% confidence intervals, at different moments of the oral glucose tolerance test.

Outcome	mean1	sd1	mean2	sd2	p-value	cut-point	95% CI	
basal	4.72	0.96	8.86	3.56	<0.0001	6.41	5.98	6.66
30min	6.85	1.68	11.34	4.10	<0.0001	9.25	8.82	9.60
60min	5.79	1.65	10.84	4.60	<0.0001	8.32	7.84	8.72
120min	5.38	1.44	11.74	5.76	<0.0001	7.96	7.55	8.24

Discussion

Since the end of last century, a bimodal distribution of glucose values—both fasting glucose and two-hour post-load— was identified in different populations, as occurred with the Pima Indians in the United States [13], the Micronesian population in the Nauru Isles [14], the Mexican Americans in San Antonio, Texas [15], the Wangela population of Papua New Guinea [16], or South African Indians [17]. In all these populations prevalence of diabetes was high at the time the study was done and the occurrence of the disease was well established. The cutoff points for diagnosing diabetes in these populations were higher than those generally used, namely ≥ 126 mg/dL (7.0 mmol/l) in impaired fasting glucose or ≥ 200 mg/dL (11.0 mmol/l) two hours after a glucose load.

The bimodal distribution of glucose values in population groups exhibiting lower prevalence levels for diabetes has also been documented in this century, such as the native population of Malaysia [2] or the Caucasian population of the United States [18]. The cutoff point found in both studies is also higher than what is currently recommended for diagnosing diabetes [3].

Recently there have been studies regarding the distribution of fasting glucose values and two-hour post-load glucose values for different populations on all five continents; in these studies, the prevalence of diabetes ranged from 1.1% in Cameroon in Africa to 2.3% in the United Kingdom, through 33.8% for the Island of Nauru to 37.8% in Egypt [2]. For these studies the cutoff points were established taking into consideration patients with a prior diabetes diagnosis and later not taking this factor into consideration. Researchers found a great variation in cutoff points for diagnosing diabetes, ranging from 6.1 to 7.2 mmol/l for fasting glucose when patients with a prior diagnosis of diabetes were not included, and 6.4 to 7.4 mmol/l when patients with a prior diagnosis of diabetes were included. At two hours post load the cutoff point ranged from 8.5 to 12.7 mmol/l for the first group and 8.2 to 13.6 mmol/l when all patients with diabetes were taken into consideration.

Based on these results, the researchers concluded that bimodal distribution, though present in different populations, did not allow for establishing cutoff points for diagnosing diabetes worldwide. Nevertheless, the fact that populations showed varying stages in the evolution of the diabetes epidemic was not taken into account.

For example, those countries in which the proportion of patients diagnosed through the survey ranged from 90 to 100% of subjects with diabetes—Greenland, Taiwan or Tonga—stood out, compared to other countries where up to 70% of subjects with diabetes knew they had it, as was the case with Egypt. While this situation may be due to the availability and accessibility of health services, it also could be explained by the fact that in some populations the diabetes epidemic is firmly entrenched, whereas in others it is evolving. It is likely that to the degree that the diabetes epidemic is well established in a given population, the two curves for bimodal distribution of glucose tend to be further apart, whereas in those populations in which the epidemic is evolving, the two curves tend to overlap more and the cutoff points are lower.

In Japan, a country experiencing a rising trend in the occurrence of diabetes [19], a cutoff point of 6.2 mmol/L has been proposed for diagnosing diabetes, well below the generally used diagnostic cutoff point [20]. Also noted in this country is that the occurrence of diabetes increases when fasting glucose values are above 85 mg/dL, and the risk of developing diabetes in 7 years' time is 2.33 times greater if the fasting glucose values range from 95 to 99 mg/dL [21]. In like manner, in Teheran it is deemed that the lower cutoff point for impaired fasting glucose of 6.1 mmol/l to 5.6 mmol/l increases the ability to predict this condition for future development of diabetes [22]. In both populations the cutoff points for fasting glucose are lower than the generally established ones.

In the Mexican indigenous population studied, the cutoff point for diagnosing diabetes, according to the bimodal distribution found, is 6.41 mmol/L, similar to that proposed in Japan [20]. The cutoff point proposed for impaired glucose two hours post-load is 8.2 mmol/L, similar to that observed in the population of India [2]. In this population in the state of Oaxaca in Mexico, diabetes was infrequent at the beginning of the century. In the communities studied there were 4 deaths due to diabetes in the 2000–2004 period, whereas for the 2005–2009 period, 10 deaths were recorded. At the same time, for the first period mentioned there were 30 new cases of the disease, whereas during the second period mentioned new cases of diabetes numbered 81—this, for a population of five communities numbering 8,429 inhabitants. Of the subjects in the study identified as having diabetes, only 32% of the men and 26% of the women knew they had

diabetes [9]. Consequently, everything points to the fact that in this population the diabetes epidemic is on the rise, thus supporting the hypothesis that the overlap of the two bimodal distribution curves and the low cutoff points are characteristic of this stage of the evolution of the disease.

The presence of the microvascular complications that are typical for diabetes with glucose values that are below the cutoff points for diabetes has led to the belief that complications may arise even before a subject has high enough blood glucose values to allow for a diagnosis of diabetes. Diabetic retinopathy is perhaps the most characteristic of microvascular complications. In the Diabetes Prevention Program (DPP), 7.9% of those pre-diabetic subjects who did not develop diabetes after an average 5.6 years suffered microaneurysms, the most characteristic lesion in diabetic retinopathy [23]. In this group of patients the average reading for fasting glucose was 5.9 ± 0.49 mmol/l and at 2 hours post-load 9.2 ± 1.12 . In the United States National Health and Nutrition Examination Survey (NHANES 2005-2006), a progressive rise in the occurrence of retinopathy was observed, starting at 5.8 mmol/l, that is, below the cutoff for diagnosing diabetes [7], a fact that has been corroborated in other populations [6].

Other microvascular complications in diabetes also show this pattern—presenting well below the current value used to diagnose diabetes (7.0 mmol/l), as is the case with neuropathy [24], and particularly so with diabetic nephropathy [24,25].

The association of blood glucose, both fasting and two-hour post-load, with the occurrence of cardiovascular disease in the population without diabetes has been broadly documented, and a recent meta-analysis has established that blood glucose levels are linked to a 19% increase in risk of cardiovascular disease, independently of the presence of other cardiovascular risk factors [26]. The risk of ischemic stroke and myocardial infarction also rises progressively based on fasting glucose levels, with the risk rising even with values below the diagnostic criteria for impaired fasting glucose [27].

The presence of chronic complications from diabetes in patients whose glucose levels are below those used in established diagnostic criteria can justify the existence of a nosological entity now known as pre-diabetes. None the less, it can also be a reflection of the lower tail of normal distribution of glucose values in subjects with diabetes that overlaps with the upper curve of normal distribution of subjects without diabetes. Bimodal distribution of fasting glucose values and post-load values characterizes the different population groups, but the cutoff point that divides both curves differs in the various populations. It is highly probable that this cutoff point is not static and that it varies within the same population based on the stage of the disease.

In the indigenous Zapotec and Mixe populations of

the state of Oaxaca, the fasting glucose values and the 2 hour post-load glucose values show bimodal distribution. The cutoff points that divide the two bimodal distribution curves are set below the cutoff points currently established for diagnosing diabetes. These values are similar to those observed in other populations where the diabetes epidemic is evolving, as is the case in this indigenous population in Mexico.

List of abbreviations

CONACYT: National Council on Science and Technology of Mexico
EM: Expectation-maximization
IFG: Impaired fasting glucose
IGT: Impaired glucose tolerance
OGGT: Oral glucose tolerance test
IMSS: Mexican Institute of Social Security
UKPDS: United Kingdom Prospective Diabetes Study

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JE contributed with the conception and design of the study, analysis and interpretation of data, drafting the manuscript. XV contributed with acquisition of data, revised the manuscript critically for important intellectual content. FP participated in analysis and interpretation of data, revised the manuscript critically for important intellectual content. MC participated in analysis and interpretation of data, revised the manuscript critically for important intellectual content. All authors read and approve the final manuscript.

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