

VALIDATION OF A NINE-FIELD TABLE ON DIABETES MELLITUS DIAGNOSIS AND MONITORING

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KEY WORDS

- DM: Diabetes Mellitus
- BFG Blood Fasting Glycemia
- EAG Estimated Average Glycemia
- HbA1c% Glycohemoglobin
- NFT Nine-Field Table

ABSTRACT

BACKGROUND: Mexico's gradual aging of population is causing epidemiological transition, with a growing incidence of chronic degenerative diseases including Diabetes Mellitus DM and several related diseases. DM is a condition that can be clinically silent for more than 10 years and that plays a central role on Public Health demanding early detection and reliable diagnosis, as a priority challenge (Ref 1,2) Major improvements occurred in diagnostic systems since 1977 when Glycohemoglobin HbA1c% was introduced in Clinical Laboratories. More than thirty years passed until this test was standardized by National Glycohemoglobin Standardization Program NGSP (Ref 2). In 2010 American Diabetes Association ADA approved HbA1c%, as a method of choice for the diagnosis of DM (Ref 3, 4) when NGSP certified methods are used.

PURPOSE: Evaluation and validation of reliability and applicability of the 3x3 Nine Field-Table, developed by MB Davidson et al (Ref 5, 6) for DM diagnosis, including BFG: Blood Fasting Glycemia, Glycohemoglobin HbA1c% and EAG: Estimated Average Glycemia, and that was modified by our group based on Mexican Statistics (Ref 7, 8, 9, 10), according to recommendations of American Diabetes Association (Ref 11, 12)

MATERIAL AND METHOD: This is clinical, semestral, tangential, observational and descriptive study involving three Clinical Laboratories located three cities of Mexico, including Guadalajara, Puebla and Merida. Ambulatory asymptomatic and apparently healthy individuals, of all ages and both sexes were invited to participate in the study. Every person was tested with single determinations of Blood Fasting Glycemia BFG mg/dL and HbA1c%. All Glycohemoglobin tests were performed using HPLC. A method that is considered as the NGSP Gold Standard. Estimated Average Glycemia (EAG mg/dL) for 90 days was calculated on each case. Interdependence of BFG, A1C and EAG was evaluated on a 3X3 matrix. In statistics, a contingency table, also known as a cross tabulation, is a format that displays multivariate frequency distribution of variables. Data were used to estimate Sensitivity and Specificity according to Bayesian Conditional Probability Theorem. (Ref 9, 10) To assure the reliability of results, all procedures were controlled under the supervision an ISO 17043:2010 Accredited External Quality Assessment Scheme. (Ref. 11)

OUTCOME: A cohort of 1,413 individuals, 56% males, with a range of 3-97 years (57+/-16.3) was included on a Data Base. Blood Fasting Glycemia BFG range was 39-402 mg/dL (116+/-39) with HbA1c% range of 3.7%-15.5% (7.0+/-1.7%). A positive correlation ($R^2=0.618$) was found between BFG & EAG. Diagnosis of DM with a BFG > 125 mg/dL with HbA1c% > 6.5% operates on a sensitivity of 91% with 62% specificity.

DISCUSSION: Quality control is the fundamental premise for medical relevance. NGSP: HbA1c% certification has strong importance on reliability and applicability, two essential criteria for the approval of any test to be used in clinical diagnosis. For DM detection is advisable to test all patients having a BFG > 125 mg/dl, even if they don't have diabetic syndrome including polyuria, polydipsia, polyphagia, weight loss or gain. Application of ADA 2009 Diagnostic Criteria using a NFT is simple and useful, when compared with Glucose Tolerance Tests (GTT). It is strongly advised that recommendations may only be applied by laboratories using Certified HPLC analytical methods since the procedure has not been validated with other alternatives for the quantification of HbA1c%. Currently, the diagnostic power of alternative systems must be considered in the uncertainty area.

CONCLUSION: According to Mexican Standard NOM-015-SSA2-2010: For Prevention, Treatment and Control of Diabetes Mellitus, HbA1c% is not recommended for diagnosis. Actually, HbA1c% is only recommended for monitoring and control. Evidence provided in this document strongly recommends the convenience of using this test, in accordance with the 2009 recommendations of the American Diabetes Association.

INTRODUCTION

Mexico is going through an epidemiological transition derived from the gradual aging of the population with an increase in chronic degenerative diseases in which DM - a problem that can be clinically silent for a period of more than 10 years - plays a central role, so early detection and reliable diagnosis is a priority challenge in Preventive Medicine and Public Health. (1,2) In Mexico, DM depends largely on the high prevalence of genetic factors in the population that, associated with socio-cultural factors during the epidemiological transition, make DM a problem of growing importance in the 21st century. It has been predicted that if action is not taken immediately, catastrophic costs will be generated that the Mexican Health System will not be able to cover, given the implicit cost of cardiovascular, neurological, blindness, kidney and other diseases. That is why, it is considered that early detection and effective prevention is also an individual challenge and task and not only a government or doctors responsibility but the entire society as a whole. The measures are diverse but in principle they should be focused on improving the quality of nutrition and physical activity to maintain an adequate weight in addition to carrying out annual timely detection campaigns that include the determination of BFG : Blood Fasting Glycemia, followed with HbA1c% determination, when a BFG >125mg/dL is found. According to Mexican Standard NOM-015-SSA2-2010: For Prevention, Treatment and Control of Diabetes Mellitus, HbA1c% is not recommended for diagnosis since is only recommended for monitoring and control. Evidence provided in this document strongly recommends the convenience of using this test, in accordance with the 2009 recommendations of the American Diabetes Association of the United States.

OBJECTIVE

The purpose of this study is to evaluate and validate the utility -which depends of reliability and applicability- of the 3x3 Nine Field-Table, developed by MB Davidson et al in 1996 (Ref 5, 6) for DM diagnosis, including BFG: Blood Fasting Glycemia, Glycohemoglobin HbA1c% and EAG: Estimated Average Glycemia, and that was modified by our group based on Mexican Statistics (Ref 7, 8, 9, 10), according to recommendations of American Diabetes Association (Ref 11, 12)

MATERIAL AND METHODS

This is a semestral, clinical, tangential, observational and descriptive work in which three Mexican Clinical Laboratories participated

- Unidad de Patología Clínica. Guadalajara
- Laboratorio Exakta. Puebla
- Laboratorio. Clínica de Mérida. Yucatan

During the first semester of 2013 ambulatory, asymptomatic and apparently healthy individuals, of all ages and both sexes were invited to participate in the study. Each individual accepted and consent to participate when tested for routine single determinations of Glycohemoglobin, HbA1c% and Blood Fasting Glycemia BFG mg/dL. HbA1c% and tests were performed using HPLC, a method that is considered as the NGSP Gold Standard. Information was documented on a data base which included automatic calculation of EAG mg/dL:

1. Data Code, Age, Sex.
2. BFG: Blood Fasting Glycemia mg/dL
3. HbA1c% Glycohemoglobin
4. Estimated Average Trimestral Glycemia. ((EAG = (A1cx30-60)

EAG : ESTIMATED AVERAGE GLUCOSE	
HbA1c%	EAG mg/dL
10.00	240
9.50	225
9.00	210
8.50	195
8.00	180
7.50	165
7.00	150
6.50	135
6.40	132
6.30	129
6.20	126
6.10	123
6.00	120
5.50	105
5.00	90
4.50	75
4.00	60
3.50	45

EAG = HbA1c X 30 - 60

FIGURE 1. Estimation of Average Glycemia for Previous Trimester. $EAG = (HbA1c \times 30) - 60$
 Ref. Terrés Speziale AM. Revista Latinoamericana de Patología Clínica 2012

In order to explore the distribution of BFG, A1C, and EAG, we developed a 3x3 Nine-Field Table NFT, (Fig. 1). A contingency table that in statistics is also known as a matrix, a type of format that displays the multivariate frequency distribution of two or more variables. Data were used to estimate Sensitivity and Specificity according to Bayesian Conditional Probability Theorem. (Ref 9, 10) for the estimation of reliability of three variables on Diabetes Mellitus diagnosis.

In medicine and statistics, Sensitivity and Specificity mathematically describe the accuracy of a test that reports the presence or absence of a medical condition. If individuals who have the condition are considered "positive" and those who do not are considered "negative", then sensitivity is a measure of how well a test can identify true positives and specificity is a measure of how well a test can identify true negatives. For all testing, both diagnoses and screening, there is usually a trade-off between sensitivity and specificity, such that higher sensitivities will mean lower specificities and vice versa.

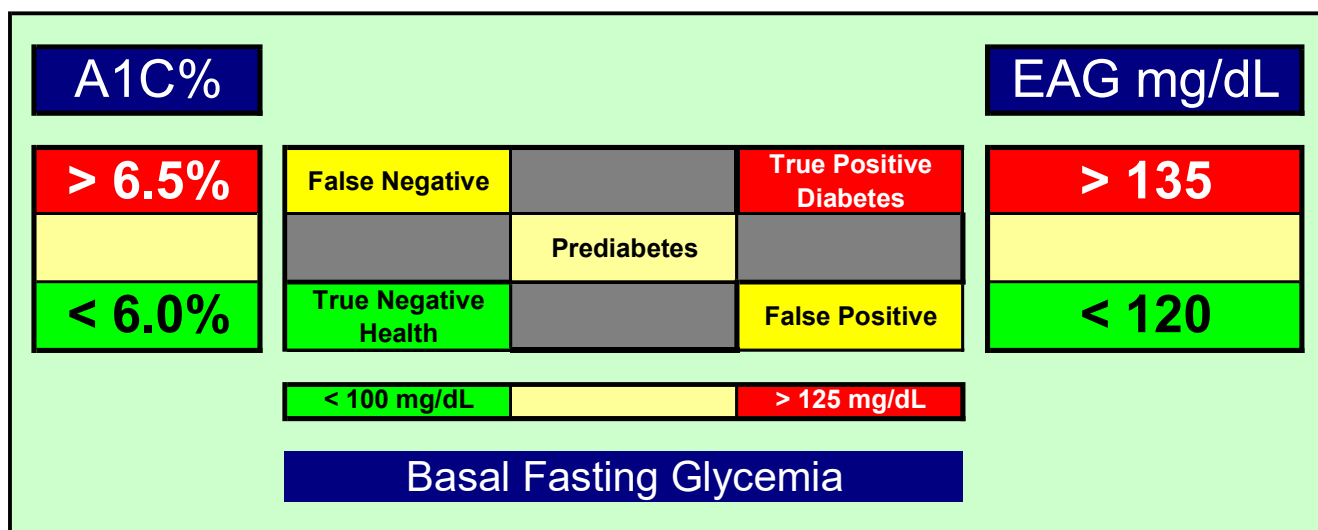


Figure 2: NFT Nine-Field Table. BFG: Blood Fasting Glycemia, EAG: Estimated Average Glycemia for Previous Trimester. Rev Latinoamer Patol Clin 2012; 59 (2): 69-79

In order to control reliability of results, all determinations were carried out with methods supervised by "EEEC QUALITAT" which is the Quality Assessment Scheme with 17043:2010 Accreditation (7). Determinations of HbA1c% were carried out with HPLC, which is considered the "Gold Standard" as it is the reference method of the National Glycohemoglobin Standardization Program (2).

RESULTS

- Figure 3: A database of 1413 results was generated from individuals ranging from 3 to 97 years of age (57 +/- 16.3).
- Figure 4: A Slight predominance of the males (56%) was found.
- Figure 5: BFG : Blood Fasting Glycemia ranged 39 to 402 mg/dL (X= 116 +/- 39)
- Figure 6: HbA1c% ranged 3.7% to 15.5% (X=7.0% +/- 1.7%)
- Figure 7: Positive correlation (R=0.618) was found between Blood Fasting Glycemia (BFG) versus Estimated Average Glycemia (EAG)
- Figure 8: Organized data according to established criteria for three levels including Diabetes, Pre Diabetes and Health. Three groups of the same magnitude were observed.
- Figure 9: Diagnostic reliability based on Bayes' Theorem estimations indicates that the diagnosis of DM with a GBA > 125 mg/dL with HbA1c% > 6.5% has a sensitivity of 91% with a specificity of 62%.
- Figure 10: Diagnostic Strategy for Diabetes Mellitus Based on a Nine-Field Table

FIGURES

FIGURE 3. Cohort of individuals included on the Data Base sorted according to age.

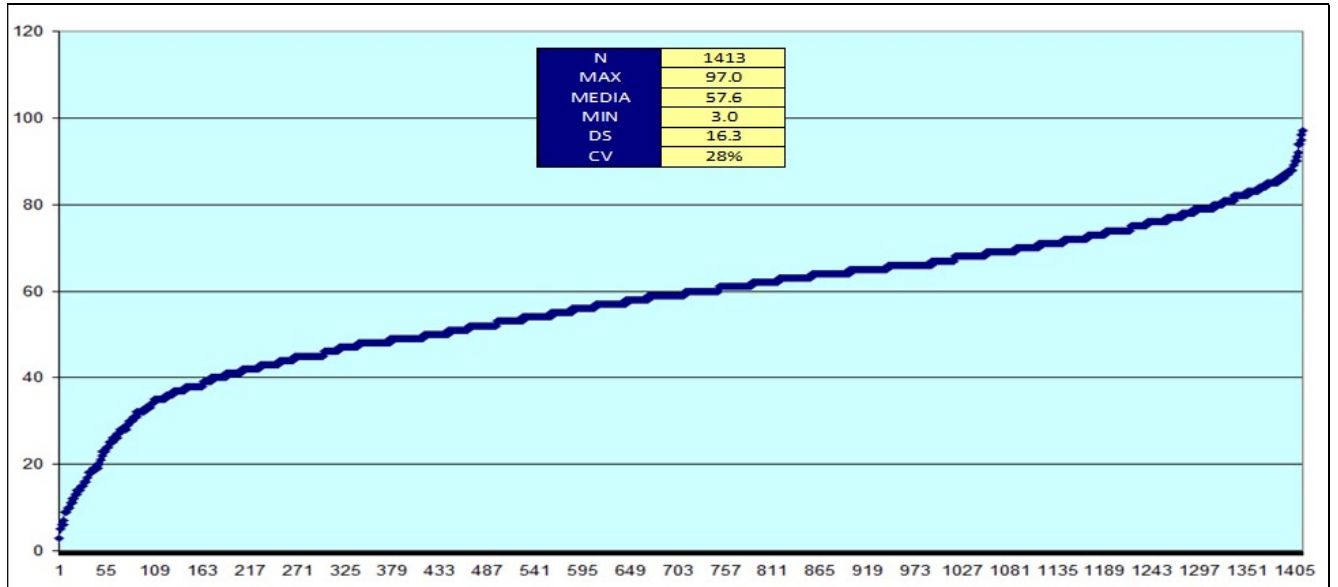


FIGURE 4. Cohort according to age and gender

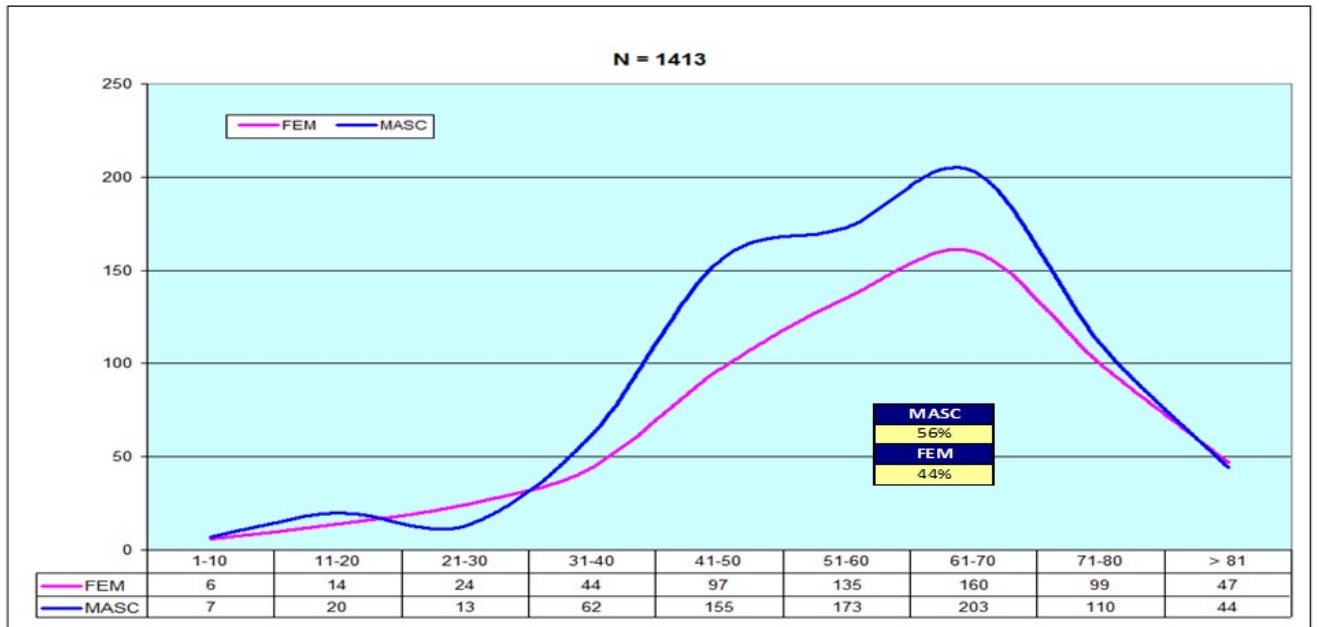


FIGURE 5. Blood Fasting Glucose BFG mg/dL according to age.

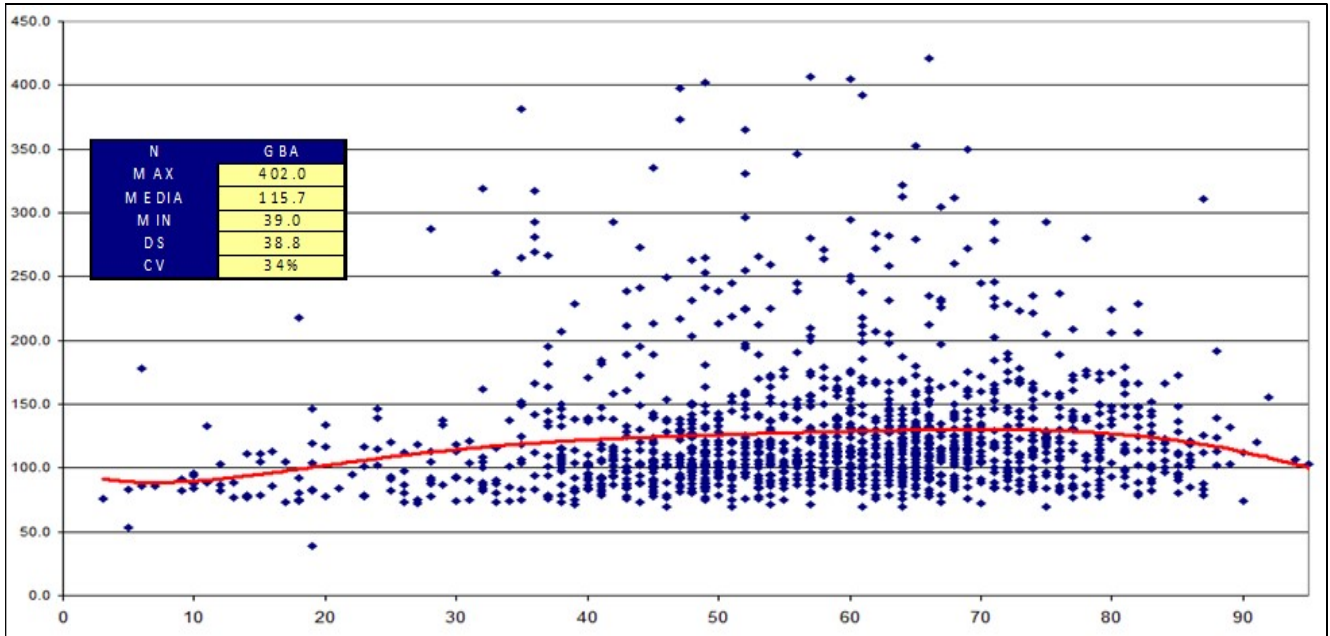
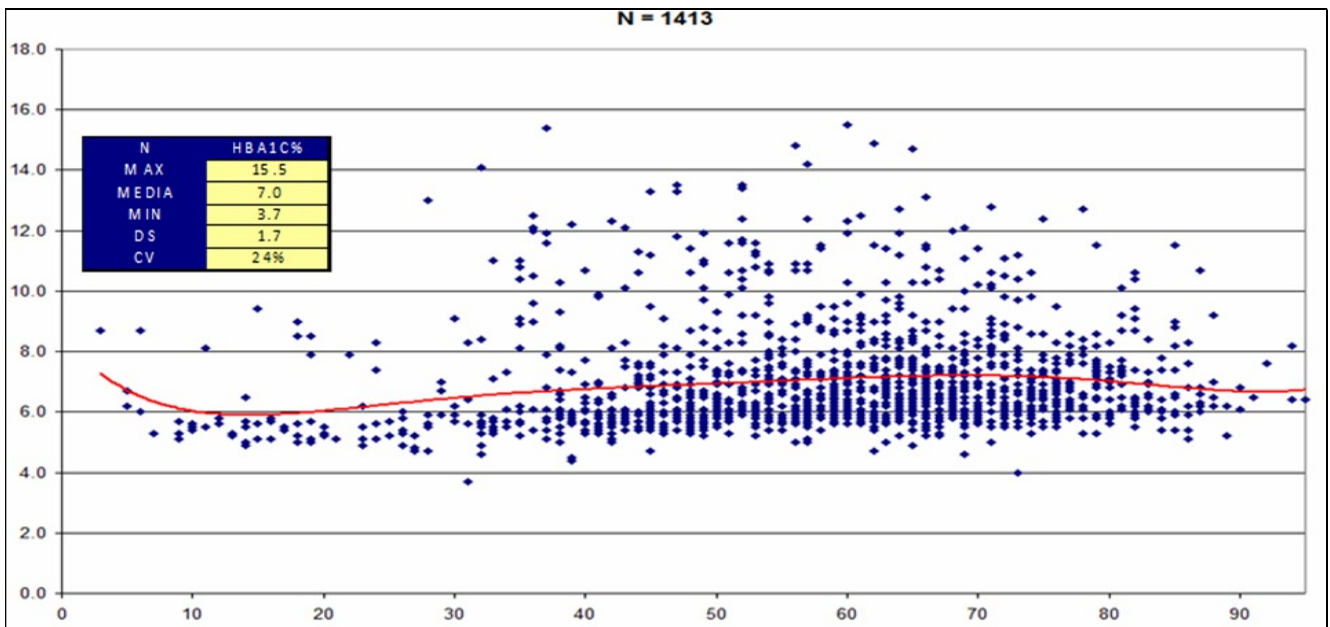


FIGURE 6. HbA1c% levels according to age.



- Figure 7: Positive correlation (R2=0.618) was found between Blood Fasting Glycemia (BFG) versus Estimated Average Glycemia (EAG = A1C X 30 – 60) for 90 days.

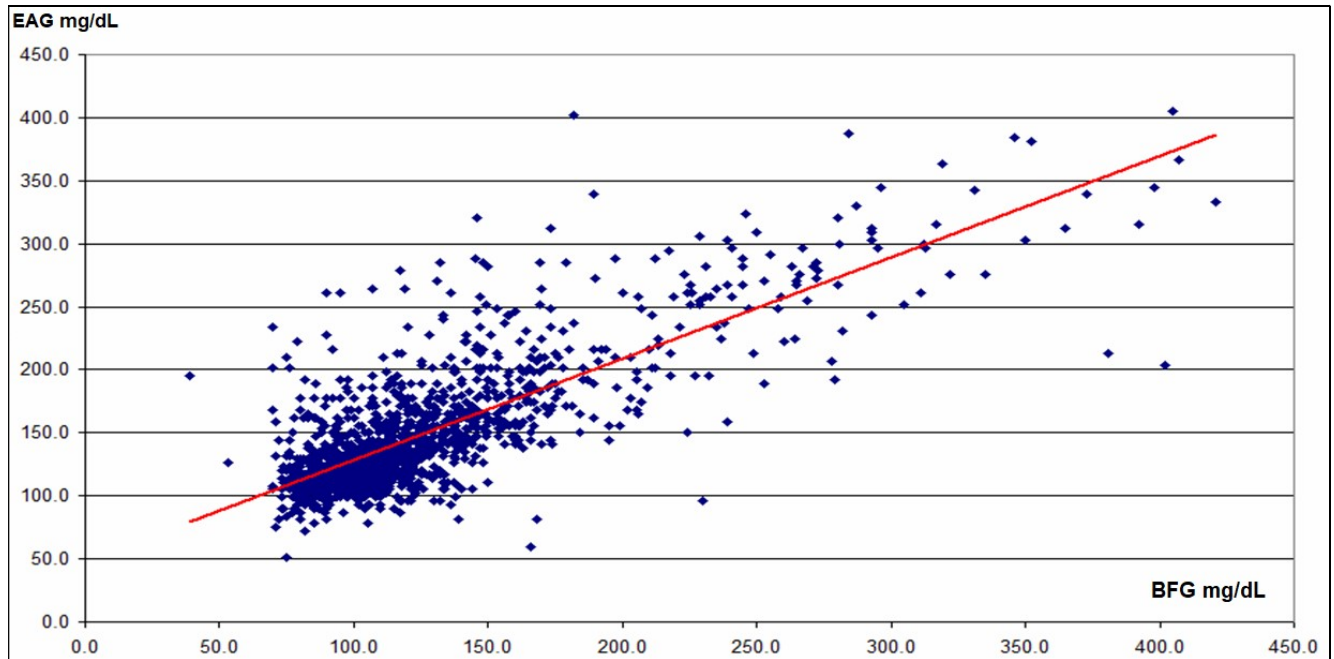


Figure 8: Data according to established criteria for three levels including Diabetes, Pre Diabetes and Health.

DATA FOR THE VALIDATION OF A NINE-FILED TABLE FOR THE DIAGNOSIS OF DIABETES MELLITUS									
CONDITION	1413	100%	Age	Male %	BFG mg/dL	BFG mg/dL	EAG mg/dL	Hba1c %	%
DM	481	34%	62	60%	> 125	177	199	> 6.5	91
			63	77%		135	129	6.1-6.4	3
			59	52%		139	106	< 6.0	6
PRE-DM	482	34%	62	53%	101 - 124	114	155	> 6.5	39
			60	52%		110	127	6.1-6.4	24
			53	60%		109	111	< 6.0	37
HEALTH	450	34%	60	53%	< 100	89	161	> 6.5	19
			61	54%		90	126	6.1-6.4	19
			56	57%		88	108	< 6.0	62
BFG = Blood Fasting Glycemia									
EAG = Estimated Average Glycemia									
Hba1c% Glycohemoglobin HPLC: High Performance Liquid Chromatography									
Dr.Arturo Manlio Terres-Speziale et al. Mexico.									

Figure 9: Diagnostic reliability based on Bayes' Theorem estimations indicates that the diagnosis of DM with a GBA > 125 mg/dL with HbA1c% > 6.5% has a sensitivity of 91% with a specificity of 62%.

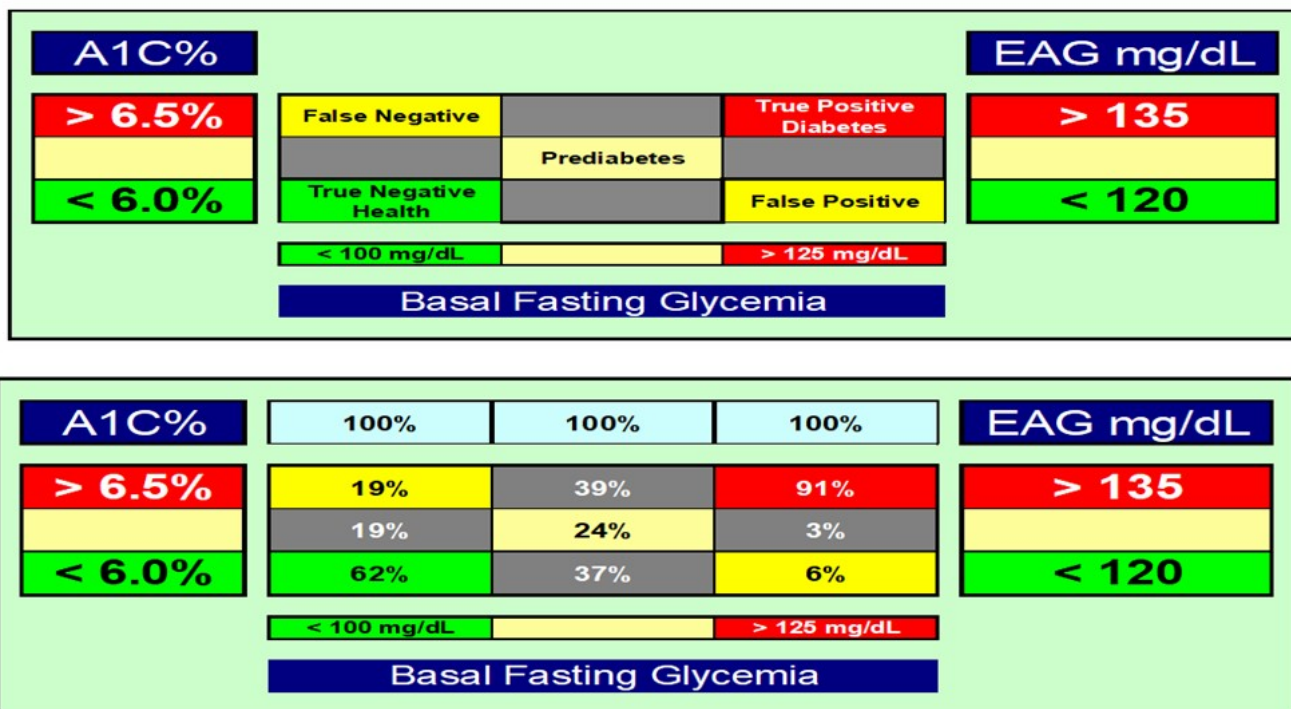


Figure 10: Diagnostic Strategy for Diabetes Mellitus Based on a Nine-Field Table

DIAGNOSTIC STRATEGY FOR DIABETES MELLITUS					
Day 1	Screening	Blood Fasting Glycemia	BFG	> 125	mg/dL
Day 2	Confirmation	Blood Fasting Glycemia	BFG	> 125	mg/dL
		Glycohemoglobin	HbA1c	> 6.5	%
		Estimated Average Glycemia	EAG	> 135	mg/dL
Dr.Arturo Manlio Terres-Speziale et al. Mexico.					

DISCUSSION

Certification of diagnostic systems by the NGSP allowed HbA1c% to reach the appropriate levels of reliability and applicability to allow the use of this test in clinical diagnosis. For the detection of DM, it is advisable to perform it in all patients who have a BFG >125 mg/dL even if they don't have a diabetic syndrome. (Polyuria, polydipsia, polyphagia, weight loss or gain). Application of ADA diagnostic criteria through NFT is very simple and useful, especially when compared to Oral Glucose Tolerance Tests. The results of this work can only be used by laboratories that use the same method and achieve the analytical control goals for Glucose and Glycohemoglobin (CV= 6.6%, CV=4.0%) (Ref.11) since the procedure in this document has not been validated with other methodologies for the quantification of HbA1c%. Diagnostic power of alternative systems must be considered in an area of uncertainty.

A final point to consider is the applicability and usefulness of the Nine-Field Table NFT in the diagnosis, surveillance and control of Diabetes Mellitus. In our experience, the location of the results of fasting Basal Blood Glucose, Glycohemoglobin HbA1c% and Average Quarterly Glucose in the 3x3 Table is more useful than the usual presentation on a report sheet, since through the graph it is possible to evaluate the patient's trends towards improvement or deterioration more clearly, which is useful for the doctor, but mainly for the patient. (Ref.12)

CONCLUSIONS

According to Mexican Standard NOM-015-SSA2-2010: For Prevention, Treatment and Control of Diabetes Mellitus, HbA1c% testing is not recommended for diagnosis. Actually, HbA1c% is only recommended for monitoring and control. Evidence provided in this document strongly recommends the convenience of using this test, in accordance with the 2009 recommendations of the American Diabetes Association.

1. Annual campaigns for Diabetes Mellitus detection should include the determination of Blood Fasting Glycemia, followed with HbA1c% determination when BFG >125mg/dL is detected.
2. NFT diagnosis in two steps may improve diagnostic efficiency while reducing costs.
3. NFT may evaluate patient's trends towards improvement or deterioration.
4. NFT is a useful tool for the diagnosis and control of DM.

BIBLIOGRAPHY

1. NORMA Oficial Mexicana NOM-015-SSA2-2010, Para La Prevención, Tratamiento y Control De La Diabetes Mellitus.
2. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, et al. The National Glycohemoglobin Standardization Program (NGSP): a five-year progress report. Clin Chem 2001;47:1985-92.
3. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-1334
4. American Diabetes Association. Diagnosis And Classification Of Diabetes Mellitus Diabetes Care, Volume 33, Supplement 1, January 2010.
5. MB Davidson: A Clinical Approach for the Diagnosis of DM An Analysis Using Glycohemoglobin Levels JAMA 1996: 276; 1246-1252
6. MB Davidson, D L Schriger, A L Peters, B Lorber: Relationship between fasting plasma glucose and glycosylated hemoglobin: potential for false-positive diagnoses of type 2 diabetes using new diagnostic criteria JAMA: 1999: 281 (13) 1203 -1210.
7. Terrés-Speziale AM. Diabetes Mellitus: Metas Six Sigma Para El Control De Calidad Analítico. Rev Mex Patol Clin 2008; 55 (1): 3-16.
8. Terrés-Speziale AM, et al. Glicemia Limites de Referencia Biocronológicos y Niveles de Decisión clínica en Población Mexicana. Rev Mex Patol Clin 1999; 46 (3): 133-142.
9. Terrés-Speziale AM. Detección, Diagnóstico Y Control De La Diabetes Mellitus Sobre La Base De Una Tabla De Nueve Campos: GBA, Hba1c, GPT. Rev Latinoamer Patol Clin 2012; 59 (2): 69-79.
10. Terrés-Speziale AM, et al. Validación de la Tabla de los nueve campos Para El Diagnóstico de Diabetes Mellitus Rev Latinoamer Patol Clin 2014; 66 (2): 70-71
11. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care 2009;32(7)1327-1334
12. Vivian Fonseca MD, Silvio E Inzucchi MD & Ele Ferranini MD. Redefining the Diagnosis of Diabetes Using Glycated Hemoglobin, Diabetes Care 2009 Jul 32(7)1344-1345

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CONFLICTS OF INTEREST: NONE DECLARED