Federal University of Rio Grande do Sul
Graduate Program in Endocrinology
Brazil

The role of glycated hemoglobin in the screening and diagnosis of renal posttransplantation diabetes

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M.S. Medical Sciences : Endocrinology

POSTTRANSPLANTATION DIABETES MELLITUS (PTDM)

Abnormal glucose metabolism that occurs after solid organ transplantation

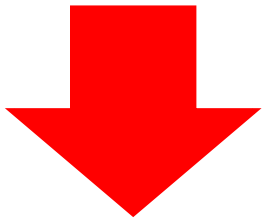
- 1964: PTDM was first documented.[1]

- Incidence in renal transplantation: 2-50%[2]

1. Surgery 1964; 56: 296.
2. Endocrinol Metab Clin N Am 36; 2007, 873–890.

RISK FACTORS: IMMUNOSUPRESSIVE MEDICATION

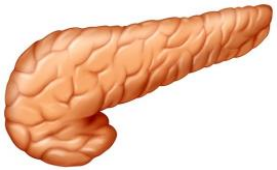
Type of immunosupressive

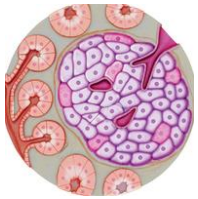


74% of the variability in the PTDM incidence

Diabetes Care 2002; 25(3):583-592

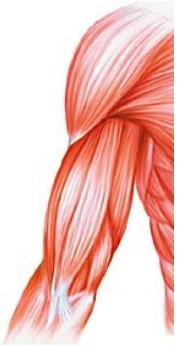
CALCINEURIN INHIBITORS
(Tacrolimus and Cyclosporine)





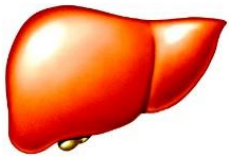
↓ INSULIN SECRETION ⇨ ↓ insulin gen expression
↑ islet cell apoptosis

HYPERGLYCEMIA



MUSCLES

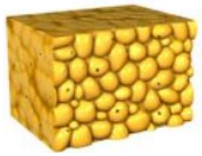
↓ Glucose uptake



LIVER

↓ Glycogen synthesis

↑ Gluconeogenesis



ADIPOSE TISSUE

↑ Visceral and central adiposity
↑ Lipolysis
↑Triglycerides

GLUCOCORTICOIDS

PTDM CLINICAL OUTCOMES

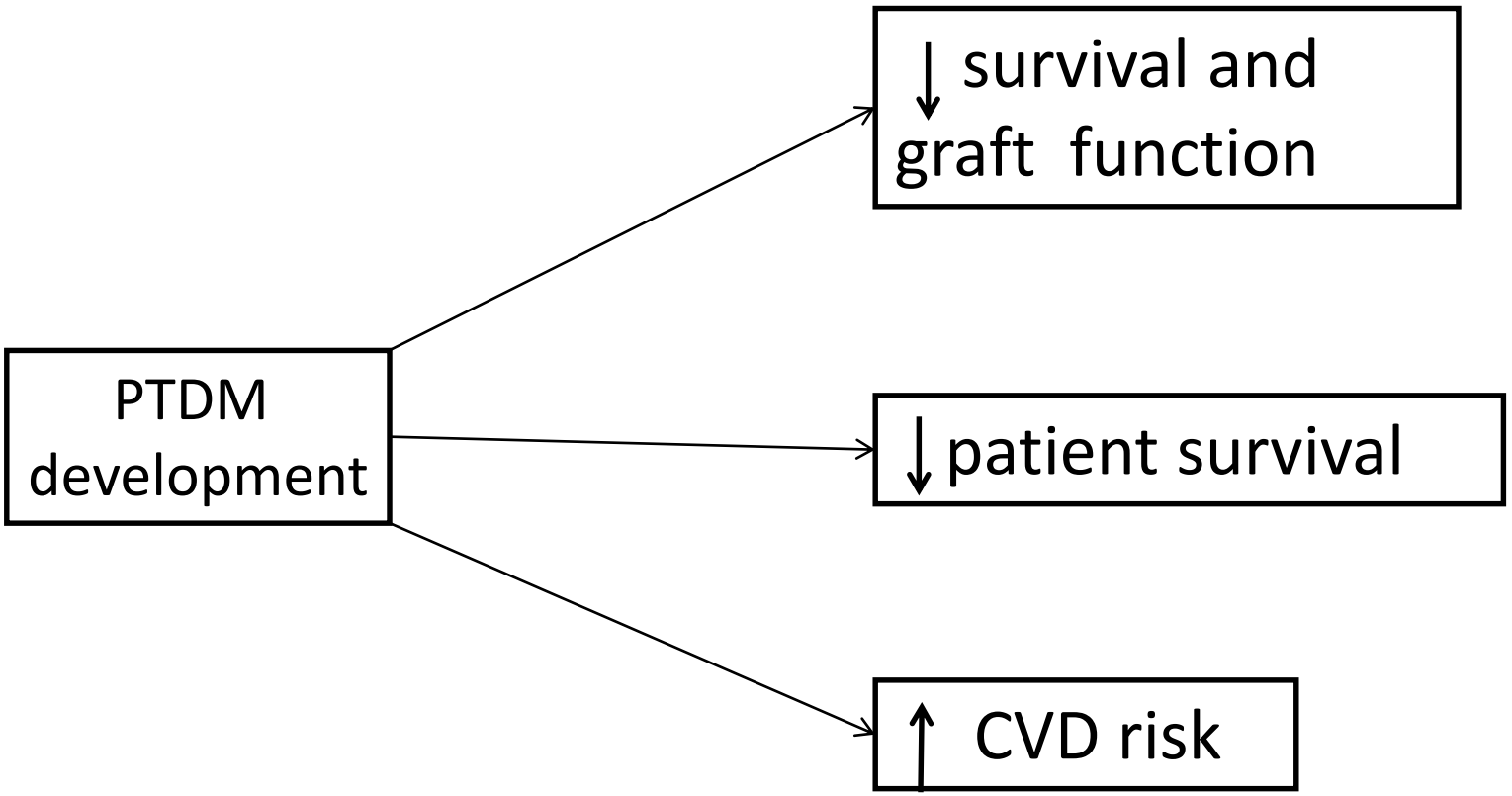
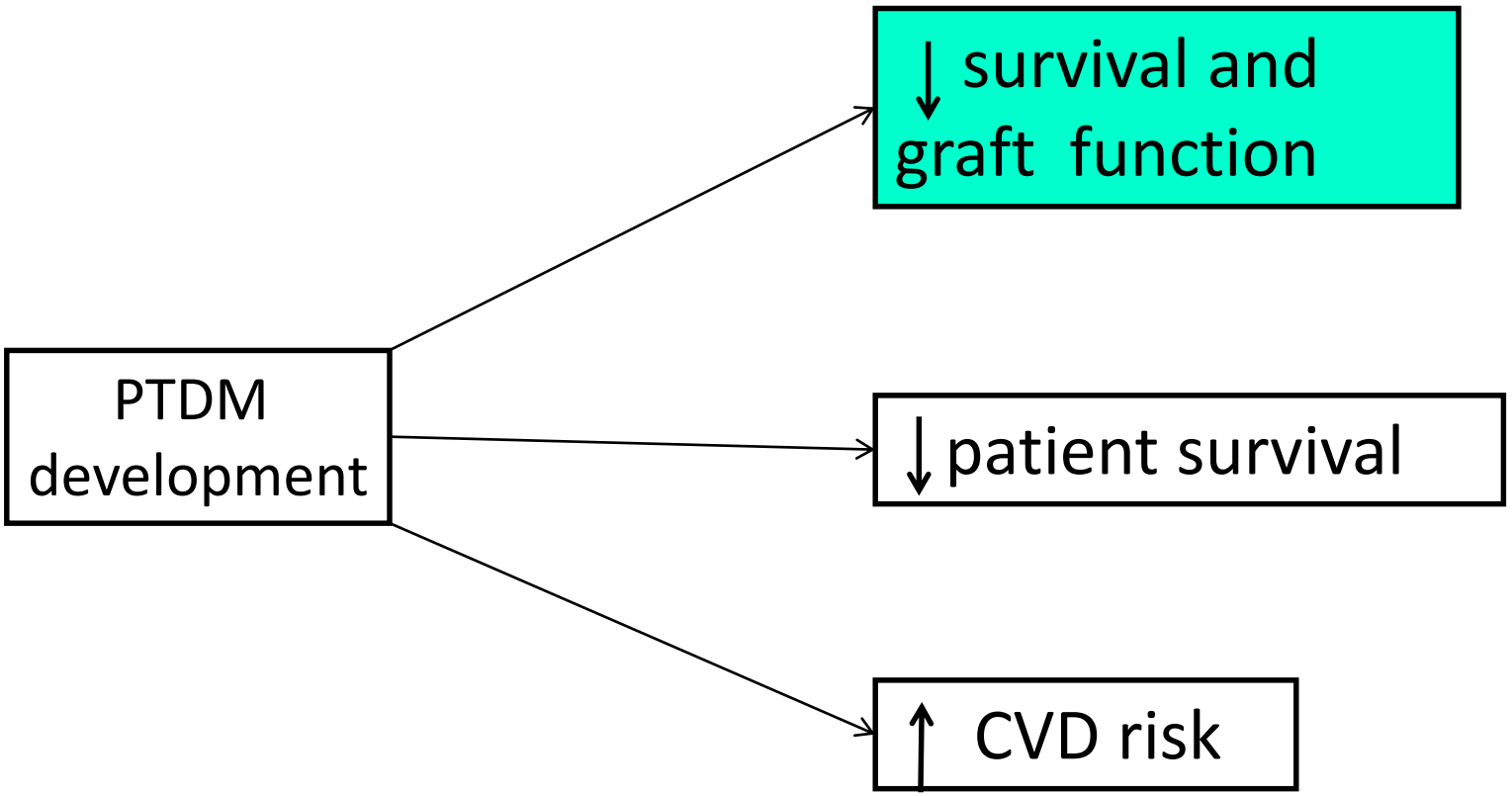


Figura 1: **Consequences of PTDM development.**

Note: Adapted from Transplantation,2003;75(10), SS3–SS24.

PTDM CLINICAL OUTCOMES



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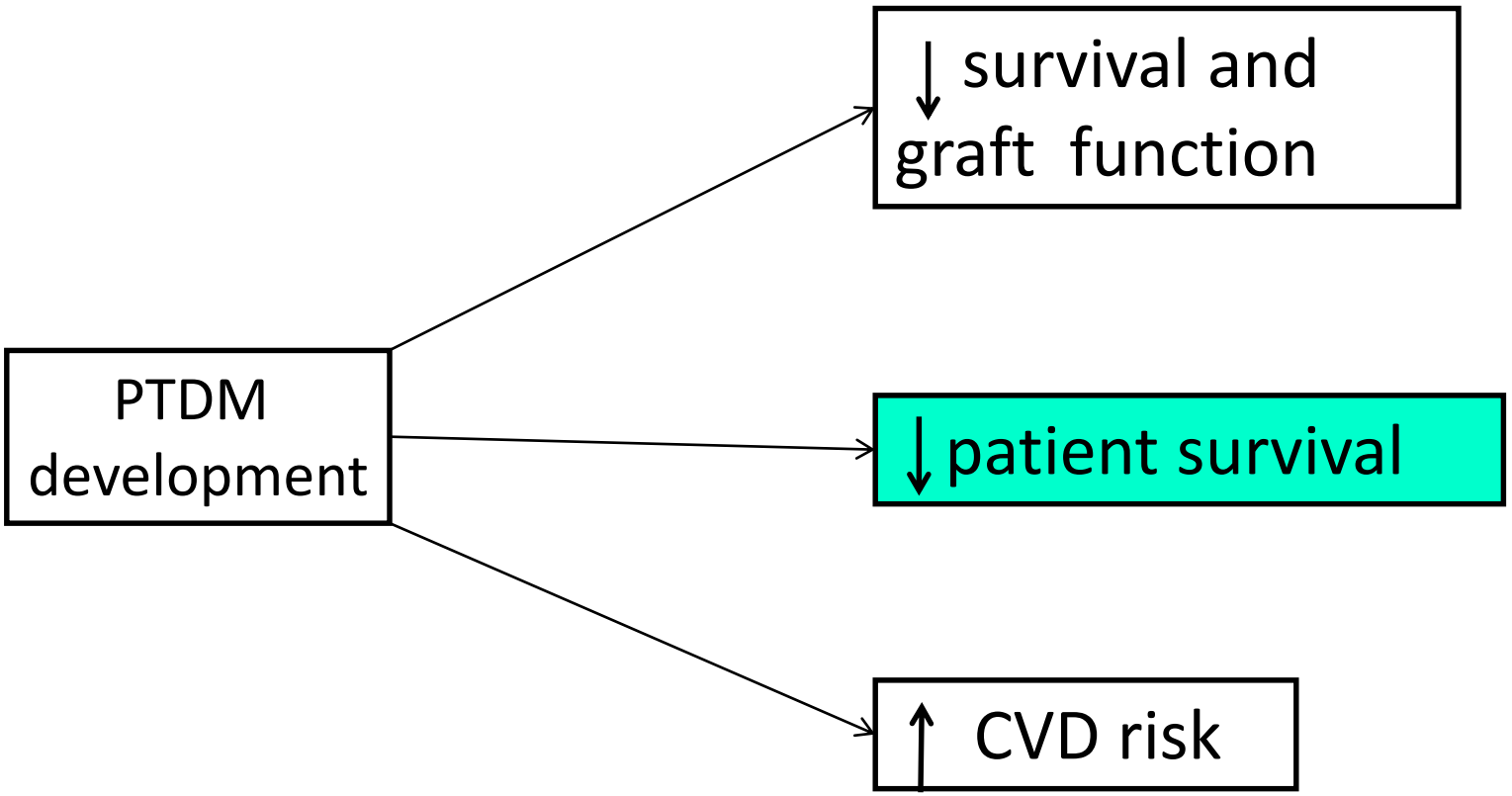

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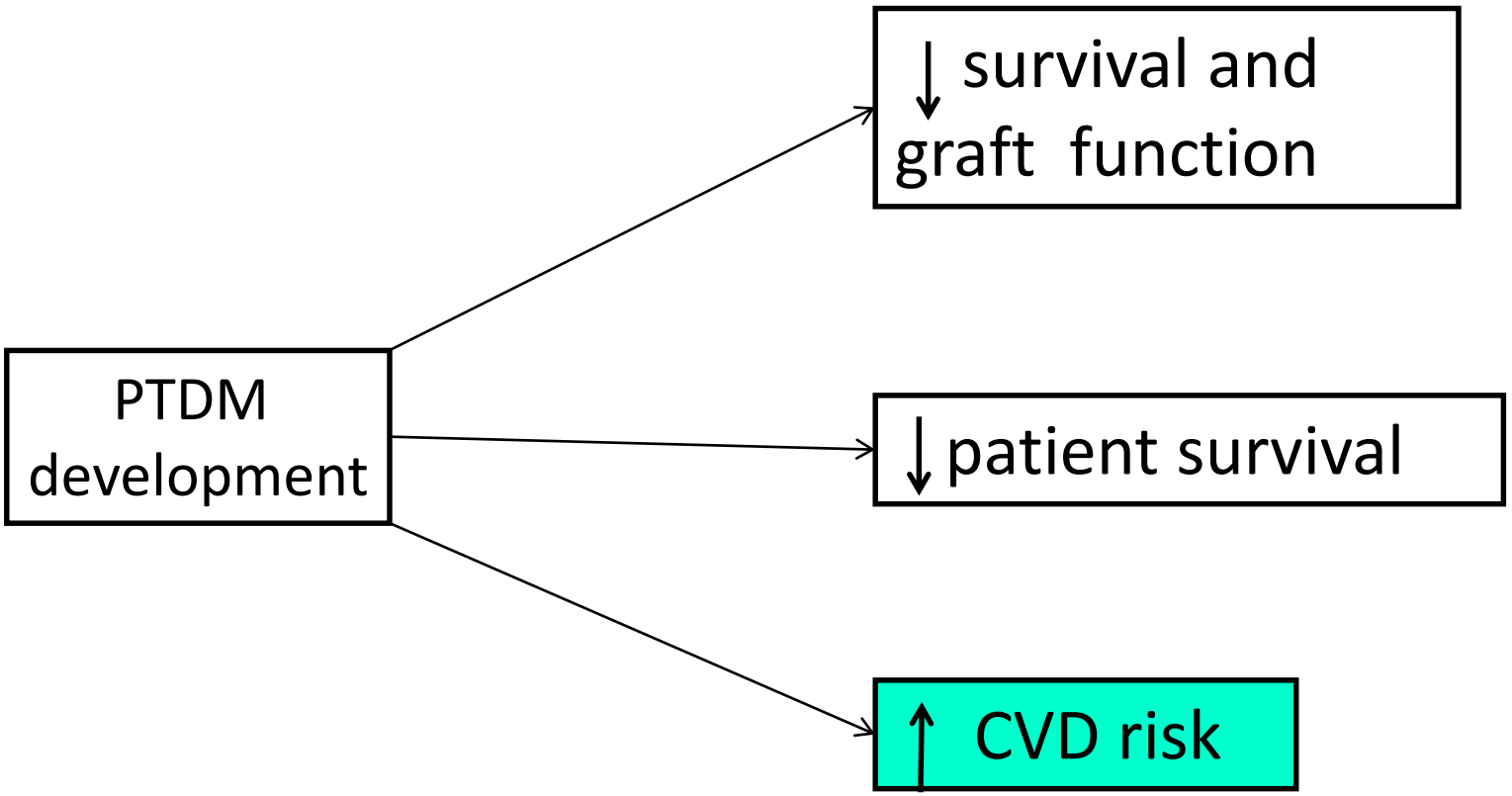

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PTDM DIAGNOSIS

Table 1: **PTDM defined by different studies**

SOURCE	DESIGN	N	PTDM DEFINITION	PTDM INCIDENCE
Revanur (2001)	RETROSPECTIVE COHORT	939	2 random-G ≥ 200 mg/dL and A1C >8% or use of hypoglycemic	5.1%
Cosio (2002)	RETROSPECTIVE COHORT	1811	Use of hypoglycemic	16.2%
Kasiske (2003)	RETROSPECTIVE COHORT	11659	Medical records	24%
Gourishankar (2004)	RETROSPECTIVE COHORT	386	2 random-G ≥ 200 mg/dL and/or 2 FG≥126 md/dL	9.8%
Gonzáles-Posada (2006)	RETROSPECTIVE COHORT	3365	2 random-G >140 or Use of hypoglycemic	7.5%

Note: Source: Nephrology, 2008; 13: 737-744.

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Note: Source: Nephrology, 2008; 13: 737-744.

Table 2: **Diagnostic criteria for diabetes and increased risk of diabetes according to ADA 2015.**

Diagnostic criteria for diabetes mellitus:
A1C ≥6.5% **OR**
FPG ≥126 mg/dL **OR**
2-h PG ≥ 200 mg/dL during an OGTT **OR**
Random plasma glucose ≥200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
Categories of increased risk for diabetes mellitus:
FPG 100 mg/dL to 125 mg/dL (IFG) **OR**
2-h PG in the 75-g OGTT 140 mg/dL to 199 mg/dL (IGT) **OR**
A1C 5.7–6.4%

FIRST CHOICE TEST: fasting glucose

Table 3: **Interfering factors in A1C results**

Reduction in A1C levels	Increase in a1C levels
Hemolytic anemias	Presence of carbamylated hemoglobin
Hemoglobinopathies	Nutritional deficiency iron
Nutritional deficiency (folic acid, B6 vitamin, B12 vitamin)	Presence of acetylated hemoglobin
Hyperthyroidism	Conditions that promote an increase in red blood cells
Severe burns	
Blood transfusion	
Erythropoietin deficiency secondary to renal impairment	

J Intern Med 2012; 271(3):227-236.
J Clin Pathol 2004;57(4):346-9.

Aim:

To evaluate the use of A1C test to diagnose PTDM and assess its overall accuracy in renal transplant recipients at four months after transplantation.

Clinica Chimica Acta 445 (2015) 48–53

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Role of glycated hemoglobin in the screening and diagnosis of posttransplantation diabetes mellitus after renal transplantation: A diagnostic accuracy study

Ana Laura Pimentel [a], Larissa Sant Anna Kellermann Carvalho [b], Samara Silva Marques [b], Rodrigo Fontanive Franco [c], Sandra Pinho Silveiro [a,d], Roberto Ceratti Manfro [c], Joíza Lins Camargo [a,d,*]

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[d] Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

MATERIALS AND METHODS

- **Diagnostic accuracy study** (STARD Initiative)

• Adult patients without DM that underwent kidney transplantation at Hospital de Clínicas de Porto Alegre between March 2012 and April 2014.

HOSPITAL DE CLÍNICAS
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Clinica Chimica Acta 445 (2015) 48-53

MATERIALS AND METHODS

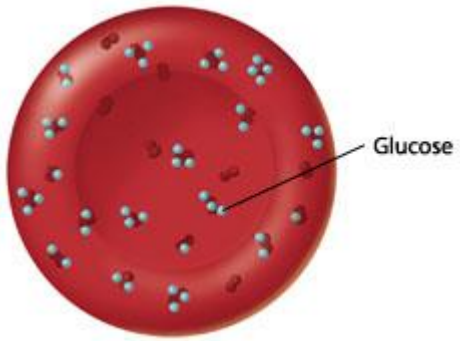
- All patients were invited to participate and to undergo an OGTT following WHO recommendations;

- PTDM diagnosis is defined by American Diabetes Association (ADA) as FPG ≥ 126 mg/dl and/or 2h-PG ≥ 200 mg/dl.

Clinica Chimica Acta 445 (2015) 48-53

MATERIALS AND METHODS

A1C: HPLC method (Bio-Rad Variant™ II Turbo analyzer), as standardized by the National Glycohemoglobin Standardization Program (NGSP) and aligned with the International Federation of Clinical Chemistry (IFCC)



Bio-Rad Variant™ II Turbo analyzer

Clinica Chimica Acta 445 (2015) 48-53

METHODOLOGY

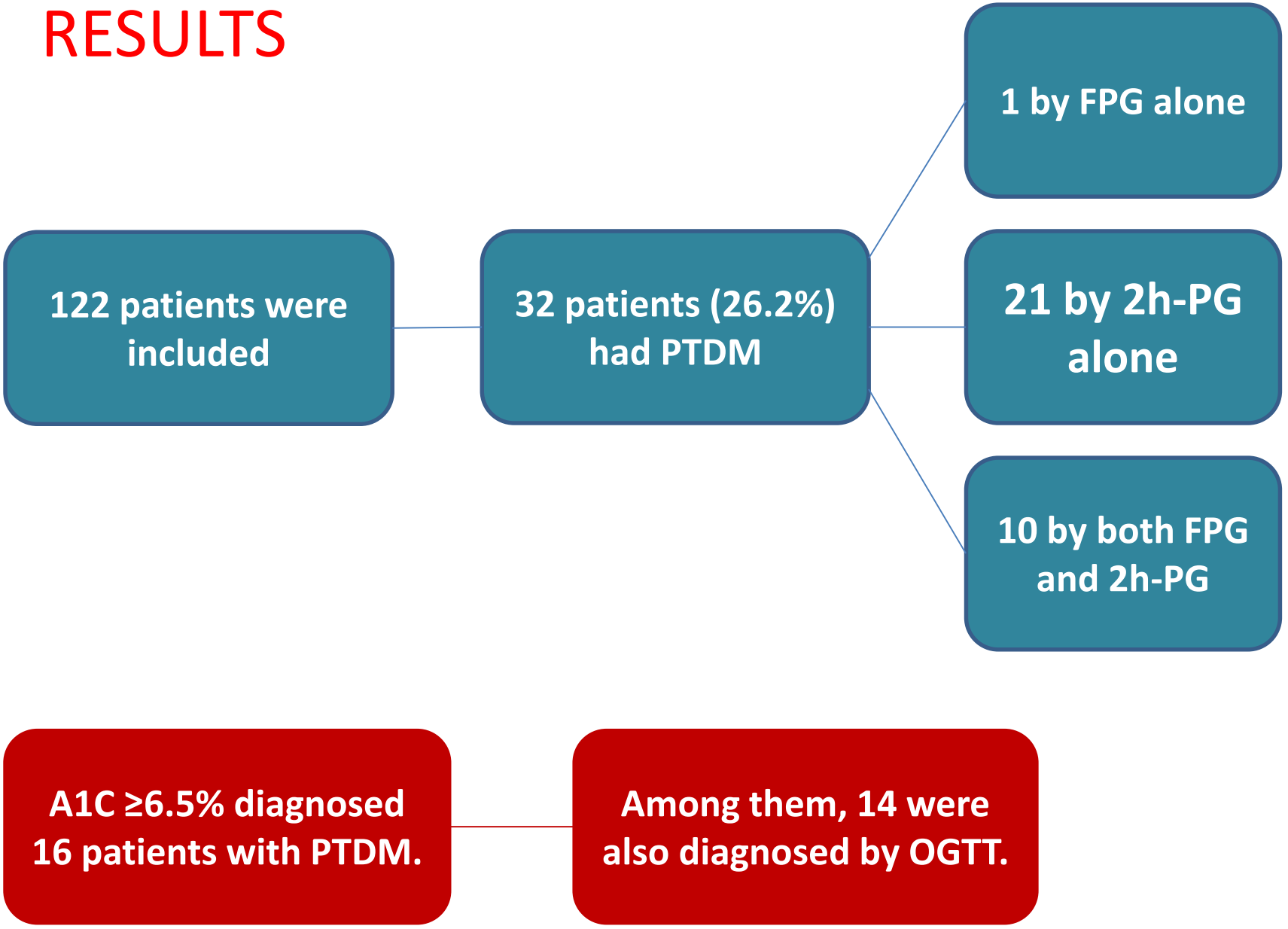
Statistical analysis

- **ROC curve:** to analyze the performance of A1C test (FPG and/or 2h-PG after an OGTT as reference diagnostic criteria).

- **Fagan nomogram:** to estimate the post-test probability of PTDM, considering the pre-test probability of 20%, estimated from the literature (clinical applicability)

Clinica Chimica Acta 445 (2015) 48-53

RESULTS



Clinica Chimica Acta 445 (2015) 48-53

Clinical and laboratory characteristics of patients in the study.

Characteristics	N = 122
Age (y)	46.2 ± 14.1
Gender (% men)	50.8
Race (% white)	73.8
Body mass index (kg/m^2)	25.8 ± 4.2
Waist circumference (cm)	94.6 ± 9.9
Systolic blood pressure (mm Hg)	126.1 ± 18.1
Diastolic blood pressure (mm Hg)	77.4 ± 10.7
A1C (%)	5.7 ± 0.8
(mmol/mol)	39 ± 8.7
Fasting plasma glucose (mg/dl)	100.7 ± 22.4
2h-PG after 75 g glucose (mg/dl)	160.2 ± 75.2
Serum creatinine levels (mg/dl)	1.63 ± 0.8
Glomerular filtration rate (ml/min)	52.6 ± 23.2
Calcineurin inhibitor use (%)	
Tacrolimus	96.7
Cyclosporine	3.3
Tacrolimus levels (ng/ml)	9.0 ± 4.3
Cyclosporine levels (ng/ml)	189.2 ± 81.7
Deceased donor (%)	82.0
Acute rejection episodes (%)	10.7
Family history of diabetes (%)	38.5
Post-transplantation time (days)	132.5 (122.0–145.0)

Data are expressed as mean ± SD, median (interquartile range) or frequencies.

RESULTS

Comparisons between patients with and without PTDM:

Variable	Without PTDM	With PTDM	P- value
Age (years)	42.8 ± 13.3	55.9 ± 11.8	< 0.001
A1C (%)	5.4 ± 0.5	6.5 ± 0.9	< 0.001
FPG (mg/dL)	92.5 ± 8.7	123.6 ± 31.8	< 0.001
2h-PG (mg/dL)	124.9 ± 38.9	260.5 ± 59.7	< 0.001

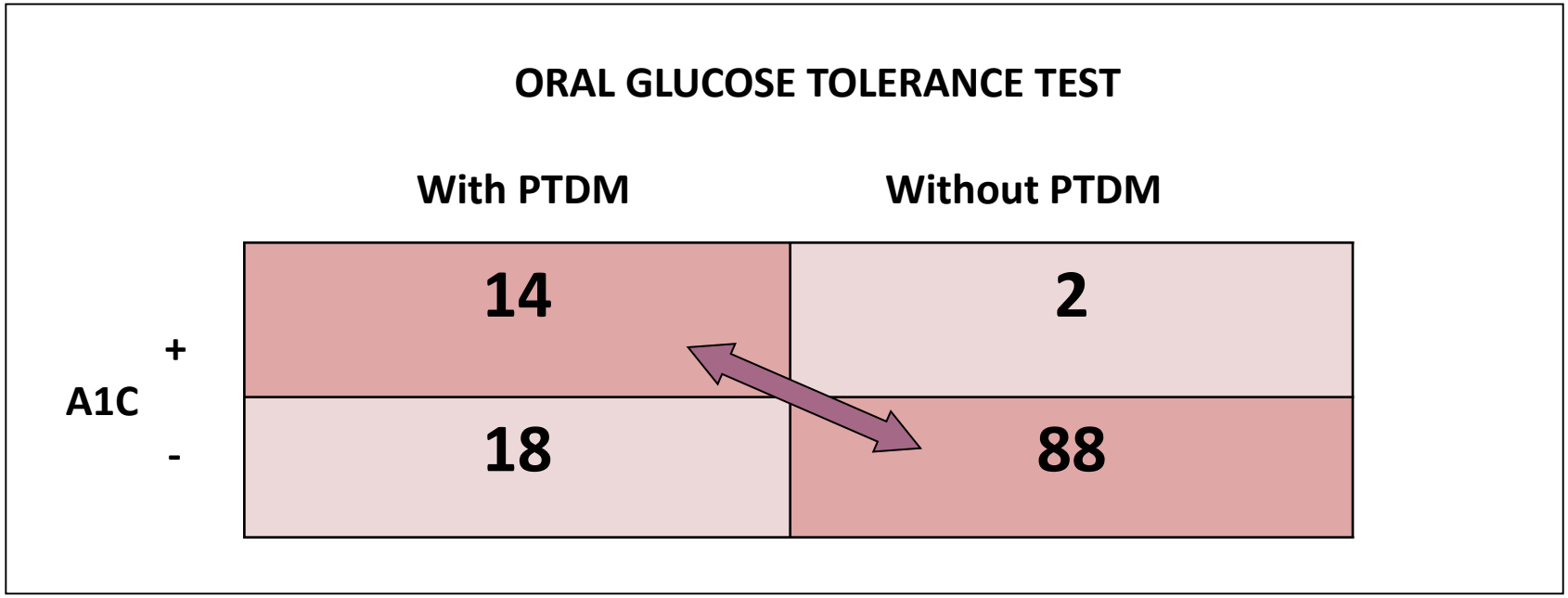
RESULTS

- **Considering A1C of 6.5%:**

SENSITIVITY: 43.7%

SPECIFICITY: 97.8%

2x2 table for A1C ≥6.5% sensitivity and specificity



RESULTS

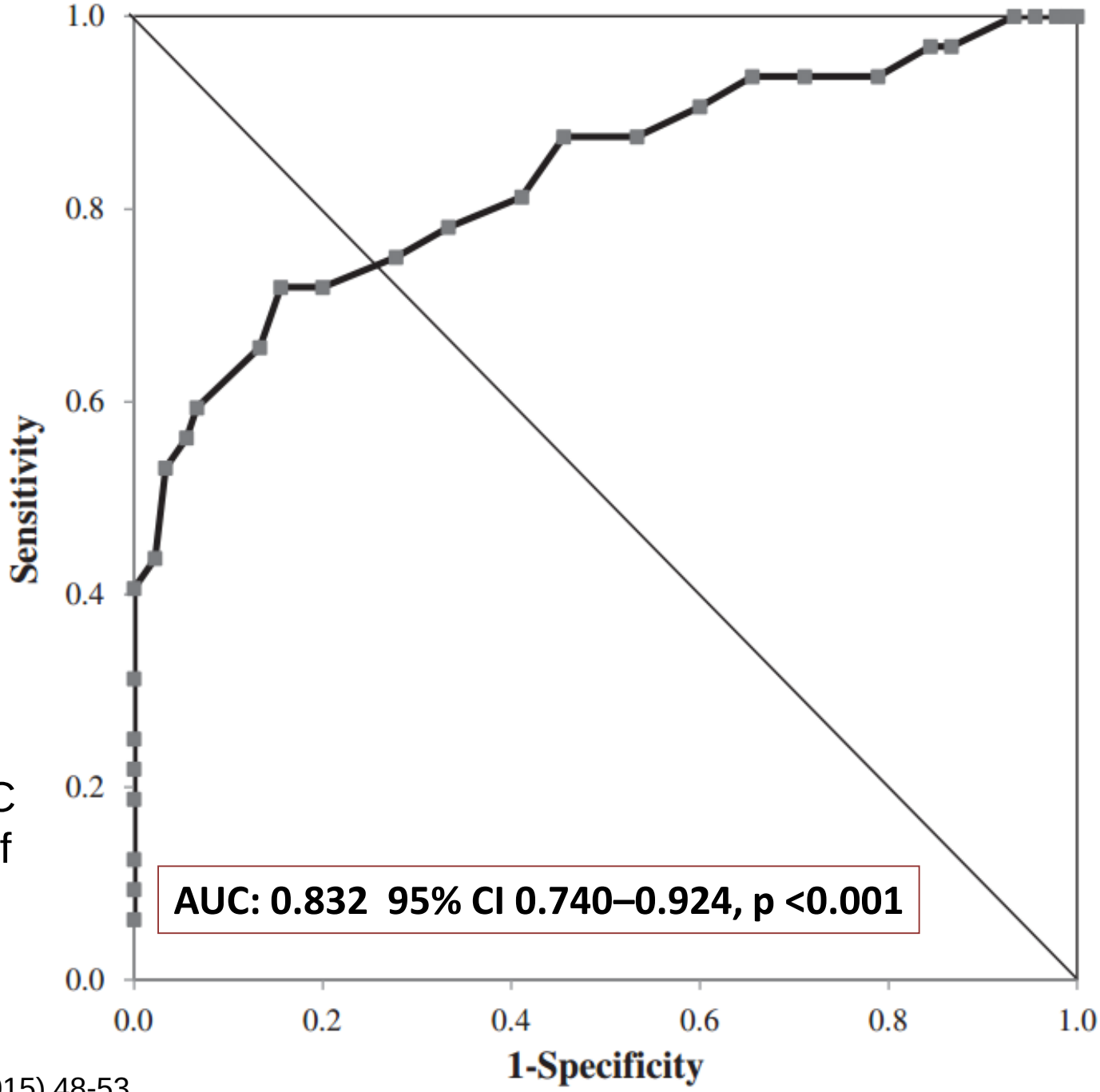


Figure 1:
ROC curve for A1C for the diagnosis of PTDM.

Clinica Chimica Acta 445 (2015) 48-53

RESULTS

Sensitivities, specificities and likelihood ratios at different A1C cut-off levels.

A1C [% (mmol/mol)]	Sensitivity (%)	Specificity (%)	LR+ (95% CI)	LR– (95% CI)
5.5 (37)	87.5	54.4	1.92 (1.48 – 2.49)	0.23 (0.09 – 0.59)
5.6 (38)	81.2	58.9	1.98 (1.47 – 2.26)	0.32 (0.15 – 0.67)
5.7 (39)	78.1	66.7	2.34 (1.66 – 3.31)	0.33 (0.17 – 0.64)
5.8 (40)	75.0	72.2	2.70 (1.83 – 3.98)	0.35 (0.19 – 0.64)
5.9 (41)	71.9	80.0	3.59 (2.25 – 5.73)	0.35 (0.2 – 0.62)
6.0 (42)	71.9	84.4	4.62 (2.73 – 7.83)	0.33 (0.19 – 0.58)
6.1 (43)	65.6	86.7	4.92 (2.75 – 8.82)	0.40 (0.24 – 0.64)
6.2 (44)	59.4	93.3	8.91 (3.91 – 20.3)	0.44 (0.29 – 0.66)
6.3 (45)	56.3	94.4	10.1 (4.10 – 25.0)	0.46 (0.31 – 0.69)
6.4 (46)	53.1	96.7	15.9 (5.00 – 50.8)	0.48 (0.33 – 0.70)
6.5 (48)	43.7	97.8	19.7 (4.73 – 81.9)	0.58 (0.42 – 0.78)
AUC:			0.832	

Clinica Chimica Acta 445 (2015) 48-53

LIKELIHOOD RATIO:

- A1C 5.8% (LR- = 0.35)

Patients without PTDM are about 3 times more likely to have an A1C value of 5.8% than patients with the disease.

$$LR - = \frac{1 - \text{sensitivity}}{\text{specificity}}$$

RESULTS

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Clinica Chimica Acta 445 (2015) 48-53

LIKELIHOOD RATIO:

A1C 6.2% (LR+ = 8.91)

A patient with PTDM is about 9 times more likely to have an A1C value of 6.2% than a person who has not PTDM.

$$LR+ = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

RESULTS

Sensitivities, specificities and likelihood ratios at different A1C cut-off levels.

A1C [% (mmol/mol)]	Sensitivity (%)	Specificity (%)	LR+ (95% CI)	LR– (95% CI)
5.5 (37)	87.5	54.4	1.92 (1.48 – 2.49)	0.23 (0.09 – 0.59)
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Clinica Chimica Acta 445 (2015) 48-53

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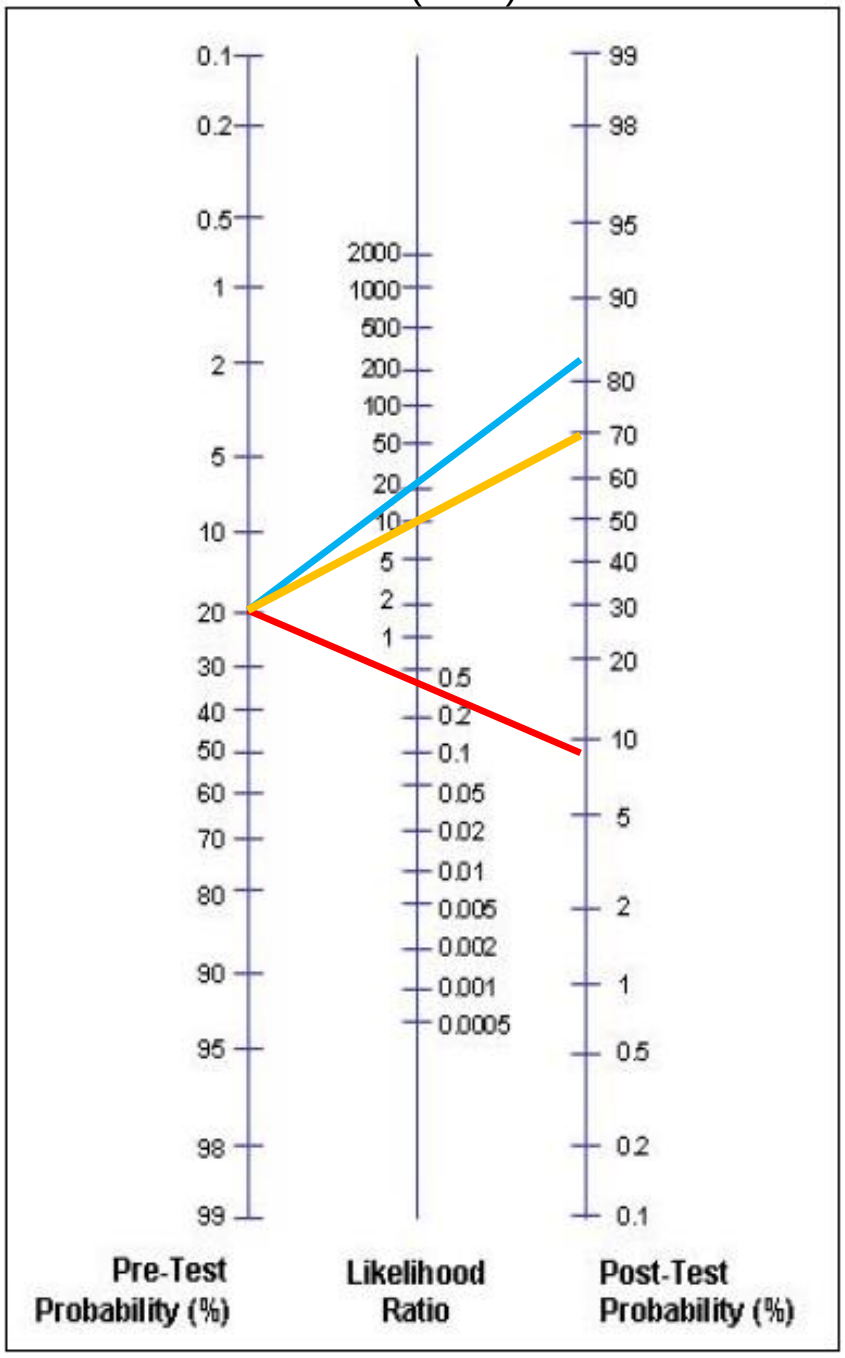


RESULTS

A1C ≥6.5% (LR + :19.7)

A1C ≥6.2% (LR + : 8.91)

A1C ≤5.8% (LR- : 0.35)

Post test probability for A1C ≥ 6.5%: 83%

Post test probability for A1C ≥ 6.2%: 69%

Post test probability for A1C ≤ 5.8%: 8%

Figure 3: Fagan's nomogram for A1C test, which showed post-test probabilities for PTDM with A1C ≤ 5.8%, A1C ≥ 6.2% and A1C ≥ 6.5%.

DISCUSSION

A1C 6.5%:

Low sensitivity → Rule out PTDM ☹

High specificity → Rule in PTDM ☺

• This point failed to diagnose half of positive cases by OGTT in our series → (16 out of 32).

- Previous studies evaluating A1C ≥6.5% to diagnose PTDM found conflicting results;

- Discrepant sensitivities were observed at A1C cut-off point of 6.5%.

First Author (Year)	PTDM incidence (%)	Number of patients	Results
Shazia (2013) 	**14.3**	**71**	Sensitivity= 83.3% Specificity= **94.4%**
Eide (2014) 	**10.3**	**1612**	Sensitivity= 38.0% Specificity= **86.3%**
Yates (2013) 	**20.0**	**50**	Sensitivity= 43% Specificity= **95.4%**
Clayton (2015) 	**29.0**	**119**	Sensitivity= 20.0% Specificity= **94.0%**
Pimentel (2015) 	**26.2**	**122**	Sensitivity= 43.7% Specificity= **97.8%**

A1C of 6.5% in the initial months after transplantation

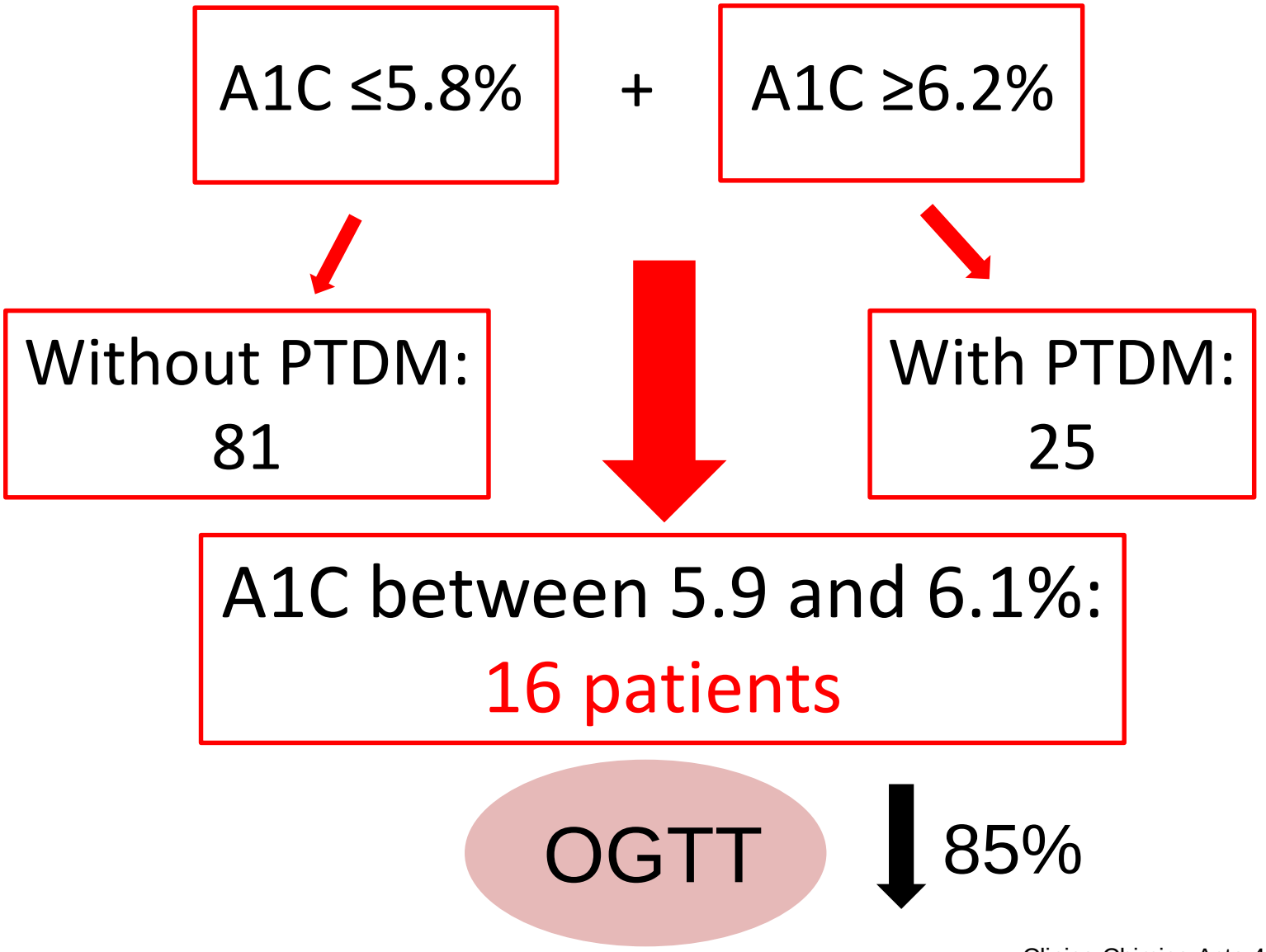
DISCUSSION

- A1C cut-off point of 5.8% presented the best balance between sensitivity and specificity and also a reasonable negative likelihood ratio (LR− = 0.35).

- A1C cut-off point of 6.2% presented high specificity.

Clinica Chimica Acta 445 (2015) 48-53

Proposed diagnostic algorithm for PTDM



Clinica Chimica Acta 445 (2015) 48-53

CONCLUSIONS

- The use of a single A1C cut-off is not enough for the screening and diagnosis of PTDM.

A1C ≥6.5%

High specificity

Ideal to be used to diagnose PTDM

(confirmation of the disease)

Low sensitivity

A lower cut-off point should be used for

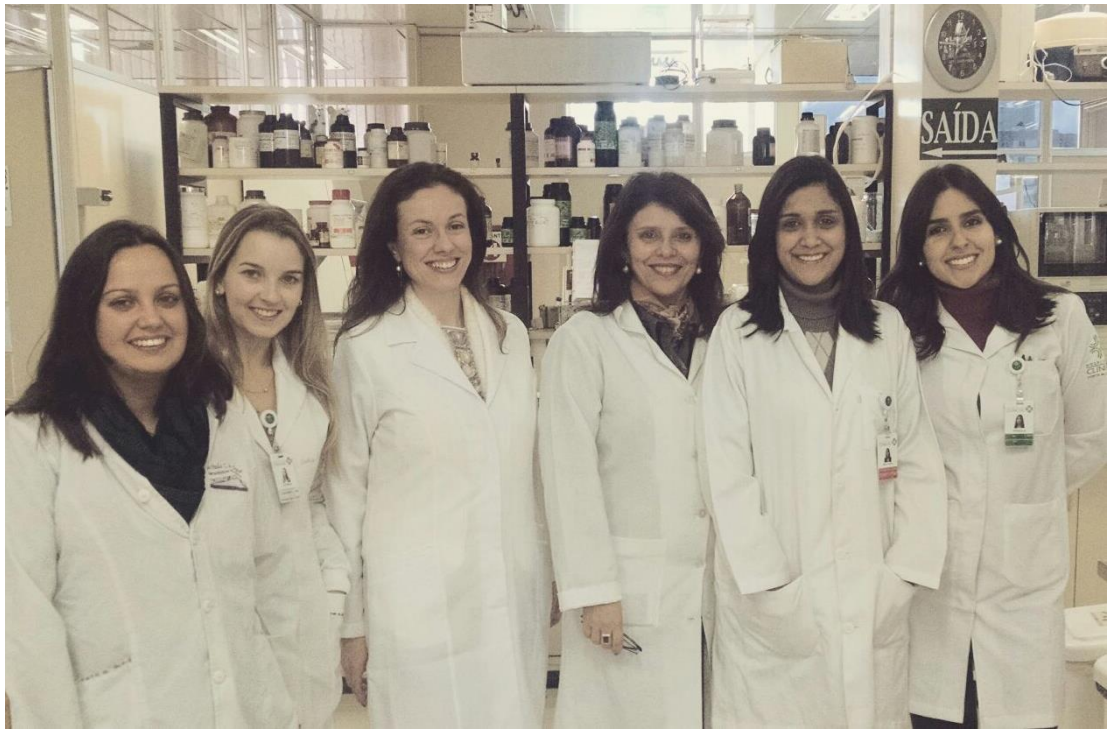
PTDM screening

Federal University of Rio Grande do Sul
Graduate Program in Medical Sciences: Endocrinology

Financial Support:

Fundo de Incentivo à Pesquisa e Eventos
HOSPITAL DE CLÍNICAS
PORTO ALEGRE RS
FAPERGS
Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul
CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES

WORKING GROUP ON DIAGNOSTIC METHODS FOR DIABETES AND ENDOCRINOLOGY



Coordinator:
Dr Joíza Lins Camargo

PhD Candidates:
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Paula Renz

Master's students:
Ana Paula Aguiar
Priscila Freitas

Undergraduate intern:
Lethicia Ehlert

THANK YOU

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