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ENDOCRINOLOGIA & DIABETES CLÍNICA E EXPERIMENTAL

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FACULDADE EVANGÉLICA DO PARANÁ

VOL. 15 - NÚMBER 3

MAY/JUNE/JULY/AUGUST/2015

Does Latin America need a new and appropriate consensus in gestational diabetes?

IADPSG 2016

The International Association of the Diabetes and Pregnancy Study Groups

21 AL 23 DE MARZO DE 2016

UNIVERSIDAD CATÓLICA ARGENTINA
Puerto Madero

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INSCRIPCIONES ABIERTAS • RESÚMENES A PARTIR DEL 24 DE AGOSTO

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CCM Worldwide Medical Congresses

EDITORIAL

THE TASKFORCE OF GESTATIONAL DIABETES IN LATIN AMERICA

Obesity can be considered an endemic global disease which leads to an increase of type II diabetes in early adulthood. Obese patients usually harbor glycemic and fatty acids metabolism diseases without even knowing these conditions. There are pregnant women with metabolic or glycemic disturbance that seek for obstetricians few months before delivery or when they are already suffering from hypertension. There are numerous cases of gestational diabetes that lack diagnosis in an appropriate time period and as a consequence, the correct treatment, leading to deleterious conditions to mother and baby.

Despite the fact that several studies have been trying to standardize gestational diabetes diagnosis and treatment through a guideline that could be globally adapted, endocrinologists still do not have a consensus in the management of gestational diabetes due to differences in populations and in social and economical resources of each country. In this context, elegant studies that have demonstrated poor outcomes as the Hyperglycemia and Adverse Pregnancy Outcome Study (HAPO) and those that have been trying to establish appropriate threshold values for gestational diabetes diagnosis as the Association of Diabetes and Pregnancy Study Groups (IADPSG) besides the controversial treatment with oral hypoglycemic agents demonstrates that Latin America needs an urgent consensus that could fit to our reality.

As a result, the Latin American Diabetes Association (ALAD) built a taskforce with the main objective of standardizing and updating the diagnosis and treatment of gestational diabetes. We have been focusing in creating a multicentric study that we believe will establish a consensus in gestational diabetes diagnosis through a cutoff point that would best suit our social reality. During the Pan American Health Organizaton for gestational diabetes study the ALAD committee defended the point of view of the taskforce. In this edition of Revista de Endocrinologia e Diabetes – Clínica & Experimental we are going to show the conferences presented by Dra. Susana Salzberg and Dra. Silvia Lapertosa from Argentina and Dra. Aldeída Rivas Blasco from Venezuela. We want to share with our readers the product of this taskforce and call for your participation in this consensus that we hope can be of great value and appropriate for our Latin America gestational diabetes population.

Editors of Revista de Endocrinologia e Diabetes – Clínica e Experimental

Contents

Endocrinology & Diabetes - Clinical and Experimental is a journal of open access that publishes case reports, original article, reviews with new insights in pathogenesis, physiology and metabolism of hormone secretion, cellular mechanisms and tissue action. This journal belongs to the Discipline of Endocrinology and Metabolism of Faculdade Evangélica do Paraná and Service of Endocrinology and Diabetes - Diabetes Unit - Hospital Universitário Evangélico de Curitiba - Paraná - Brazil

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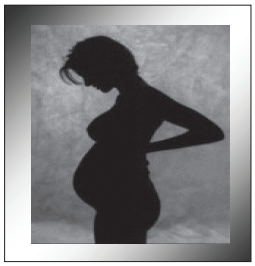
CDD 616.4
CDU 612.34

The Task Force of Gestational Diabetes in Latin America

Detección y Diagnóstico de la Diabetes en el Embarazo



Dra Susana Salzberg

Coordinadora del Grupo de Trabajo "Diabetes y Embarazo" Asoc Latinoam. Diabetes

Asesora del Comité de "Diabetes y Embarazo" Soc. Arg. Diabetes

Integrante de Federación Internacional de Ginecología y Obstetricia (FIGO)

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Diabetes Gestacional : Alteración de la tolerancia a la glucosa de severidad variable que comienza o se diagnostica en el presente embarazo

POBLACION HETEROGENEA

Metzger B. Diabetes Care 1998;21 (suppl 2):B161
ADA Position Statement . D Care 2009

Criterio de dx fue definido para identificar mujeres con mayor riesgo de diabetes en el futuro
O´Sullivan y Mahan Diabetes 1964;13:278

.....Y no para evaluar riesgo de resultados perinatales adversos .

Diabetes Gestacional : Alteración de la tolerancia a la glucosa de severidad variable que comienza o se diagnostica en el presente embarazo

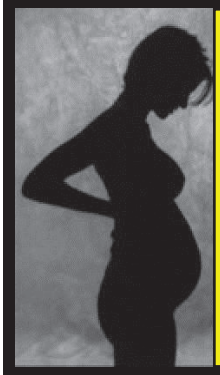
POBLACION HETEROGENEA

Metzger B. Diabetes Care 1998;21 (suppl 2):B161
ADA Position Statement . D Care 2009

subgrupo de embarazadas con hiperglucemia desde 1° trimestre → DM no diagnosticada ????

Embarazadas con glucemia s < a los valores de dx tenían complicaciones perinatales

Implicancias de la Hiperglucemia Materna



Hiperglucemia → hiperglucemia → COMPLICACIONES HMD

- período embriogénico (primeras 8 sem) → Malform. Congénitas y Abortos Espontáneos
- período fetal → Macrosomía, Sdme Distress Resp, Hipoglucemia neo

Pedersen J. Acta Endocrinol 1954;16:330–42.

DIABETES en el EMBARAZO

ASINTOMATICA EN LA MADRE

EN QUE EMBARAZADAS LA BUSCAMOS ?

En qué momento del embarazo ?

EN TODAS Priorizando las que tienen FR

Mejor relación costo/beneficio global: ahorro de U$S 833.870/año

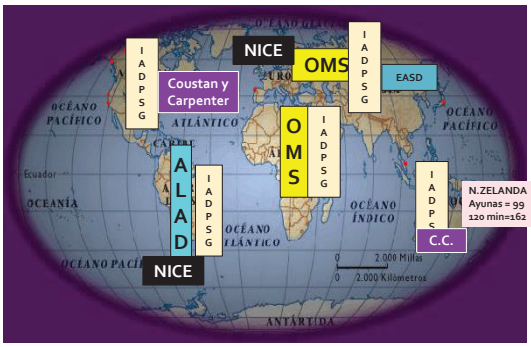
ALGORITMO DE DX DE DIABETES EN EL EMBARAZO

- Primera consulta prenatal glucosa plasmática en ayunas
  - ≥ 126 → Repetir en la semana → ≥ 126 → DIABETES PREGESTACIONAL
  - ≥ 200 + síntomas → DIABETES PREGESTACIONAL
  - < 100 → 24 - 28sem. PTOG

A1c >6.5% sólo ADA

IADPSG 2010
OMS 2013
ALAD 2013

DIABETES GESTACIONAL
CONTROVERSIAS EN CRITERIOS DE Dx



Mukesh M Agarwal *World J Diabetes* 2015 ;6(6): 782

Estudio internacional prospectivo, observacional, multicéntrico, doble ciego, enroló 25.500 embarazadas (p75 en 3er T)

Objetivo: evaluar riesgo de complicaciones maternas y feto-neonatales asociadas a niveles de glucosa materna

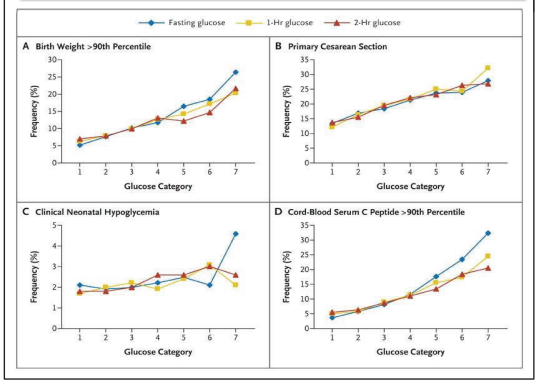
HAPO

Hyperglycemia and Adverse Pregnancy Outcome Study

Metzger BE.HAPO Study .NEJ Med 2008; 358:1991-2002

ESTUDIO HAPO
Relación entre niveles de glucemia y complicaciones

n=25500



Metzger BE.HAPO Study .NEJ Med 2008; 358:1991-2002

cómo extrapolar los resultados del ESTUDIO HAPO a la práctica para hacer dx DG ?

IADPSG estableció como punto de corte : nivel glucémico en el cual las tasas de los eventos fetales ↑ 1,75 veces sobre la media de la población del estudio (no participarn centros de latinoamérica)

Metzger BE.HAPO Study .NEJ Med 2008; 358:1991-2002

ACOG 2011 y Consenso NIH 2013

- Aumenta significativamente la prevalencia del DG
- Sin evidencia de mejores resultados feto-neonatales o en madre
- Se triplica el costo anual destinado a DG
- Se desconoce la relación costo/beneficio

Obst Gynecol 2013;122:358

OMS 2013
ADHIERE A LA RECOMENDACIÓN DEL IADPSG.

Aclara :
Calidad de la evidencia = muy baja
Fuerza de la recomendación = débil

Overview of the different international recommendations for screening for GDM

WHO	➢ IADPSG criteria for GDM
Endocrine Society	➢ One-step screening strategy with IADPSG cx
ADA → IADPSG	**Option between:** ➢ One-step screening strategy with IADPSG criteria **Or**
ADA → American College Obst Gynecol	➢ Two-step screening strategy with 50 g GCT and 100 g OGTT with the Carpenter & Coustan criteria or the NDDG criteria
NIH =National Institute of Health	➢ Two-step screening strategy with 50 g GCT and 100 g OGTT with the Carpenter & Coustan criteria or the NDDG criteria
SOCIEDAD CANADIENSE DE DIABETES	➢ Two-step screening strategy with 50 g GCT and 75g OGTT **DIFERENTES PUNTOS DE CORTE**

Benhalima *et al. BMC Pregnancy and Childbirth* 2014 14:226

GUIAS NICE 2015
National Institute for Health and Care Excellence

GLUCOSA PLASMATICA EN AYUNAS ≥ 5.6mmol/litre =100 mg/dl

or

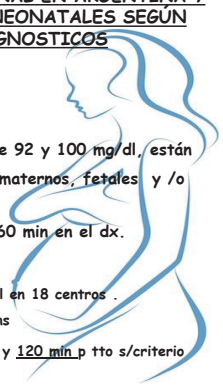
GLUCOSA PLASMATICA 2 hs POSTCARGA ≥ 7.8mmol/l =140 mg/dl

Coincide con la propuesta de ALAD 2007 y SAD 2008 que seguimos utilizando como criterio dx

Prevalencia de D.G de los otros criterios comparados con IADPSG

Investigador	n	IADPSG	ADA Coustand y Carpenter	ALAD
Estudio HAPO	25505	16.1% *	+ 100% 7%	
Hojman J. 2012 (Hospital de Clínicas San Martín)	913	6.83%	50% 4.6%	
Schmidt MI (Brazilian Gestational Diabetes Study)	4.977	17.8%	+ 200%	7.2%
Glatstein L,2012 (Hospital M.I. de Córdoba)	500	36.5% (46% dx en ayunas)	Casi 300%	13%
Hod M. 2012 (Univ de Tel-Aviv)	3345	9%	50% 6%	
SAD,2014 (reporte preliminar)	927	26.7%	158 %	10.3%

PREVALENCIA DE DIABETES GESTACIONAL EN ARGENTINA Y COMPLICACIONES MATERNO-FETO-NEONATALES SEGÚN DISTINTOS CRITERIOS DIAGNOSTICOS



Objetivo

- Evaluar prevalencia de DG
- Investigar si niveles de glucemia ayunas entre 92 y 100 mg/dl, están asociados a > riesgo de resultados adversos maternos, fetales y /o neonatales
- Establecer qué valor tiene la glucemia a los 60 min en el dx.

Metodología

n= 4000 gestantes que concurran a control prenatal en 18 centros .

24-28 semana :p75 con 3 puntos =ayunas , 1 y 2 hs

- Se tratarán las pacientes con glucemia en ayunas y 120 min p tto s/criterio ALAD
- 60 min = ciego

SAD 2014

COSTO COMPARATIVO DE TIRAS REACTIVAS ALAD vs IADPSG

	ALAD	IADPSG
PREVALENCIA	**10.36%**	**26.7%**
1.000.000 PARTOS /AÑO	**DG = 103.600/año**	**DG= 267.000/año**
VPP para MACROSOMIA	**11.46%**	**10.67%**
Tiras x día (3)	**310.800**	**801.000**
Cajas x 50 tiras/día	**6.216**	**16.020**
Cajas en 10 semanas	**435.120 frascos**	**1.121.400**
Costo en USD	**USD 13.053.600**	**USD 33.642.000**

2014

Criterio dx DG IADPSG

- N° de visitas prenatales al obstetra
- Diabetólogo
- Dietista
- Educador en diabetes
- N° de cesáreas
- Dias de interna

Costo anual en DG aumenta de USD 636 millones á 2 billones

NIH Obst Gynecol.2013;122:358

Nuestros países latinoamericanos tienen recursos limitados con prioridades sanitarias

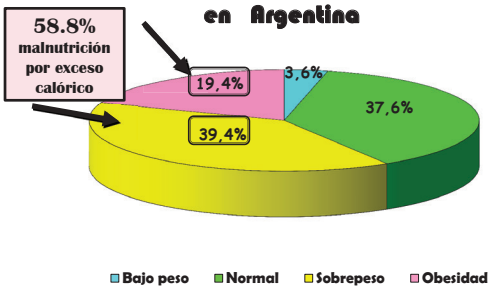
invertir en frenar la epidemia de obesidad nos lleva a reducir la DG y la DM2

ALTO PESO PARA EDAD GESTACIONAL RELACION CON OBESODAD y DG con APEG

	n	n APEG	%	OR
EMBARAZADA NORMAL	17.244	1.339	7.8	1
DG (no obesa)	2.791	401	14.4	1.99 (1.77–2.25)
OBESA (no DG)	2.247	278	12.4 1	1.73 (1.50–2.00)
GD + OBESIDAD	935	203	21.7	3.29 (2.79–3.89)

HAPO Study Catalano P. D. Care,2012 ;35:780–786

Estado nutricional de las embarazadas en Argentina



Encuesta Nacional de Nutrición y Salud ENNyS, 2007

* Estimado por IMC según curva Rosso-Mardones

Factores asociados al peso del RN en mujeres normales con parto a término

n = 83

Variables	RR	p
Peso previo al embarazo	7.26	0.01
Triglicéridos	4.07	0.01
Ganancia de peso	3.16	0.08
Glucosa plasmática (PTOG 120 minutos)	1.70	0.09

Di Cianni R y col. Diabetic Medicine 2004; 22: 21-25

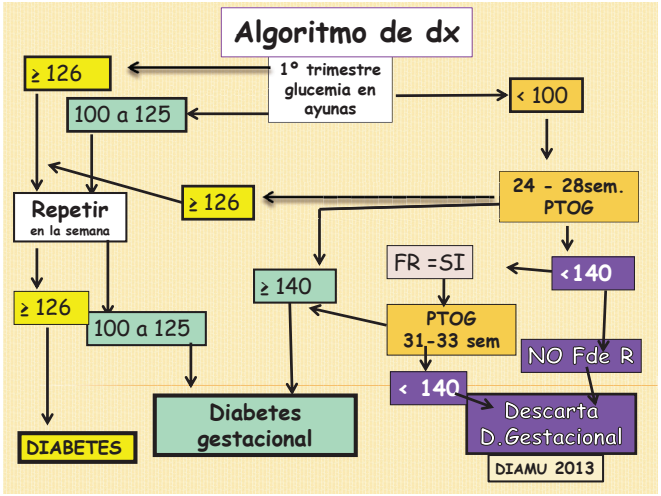
Por qué el Grupo de Trabajo Diabetes y Embarazo ALAD decidió NO INNOVAR hasta tener nuestros resultados ?

- En el HAPO no participaron centros de latinoamerica, donde hay etnias diferentes.
- El HAPO es un estudio excelente, pero el punto de corte para dx DG no surge en forma directa del estudio.
- Aumenta significativamente la prevalecia. Relación costo/eficacia ?
- se evaluaron glucemias del tercer trimestre, que son más bajas; extrapolando ese valor a todo el embarazo.

Recomendación de prevención primaria DG

Embarazadas con obesidad y que presentan glucemia en ayunas de ≥ 85 a 99 mg/dl, son pacientes de riesgo y deben tener un seguimiento con plan de alimentación y actividad física, sin intervención farmacológica con el fin de prevenir diabetes gestacional.

(Etchgoyen G. Et al. CENEXA. Prodiaba Rev medicina 2000)



TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO


ALEIDA RIVAS BLASCO
Unidad de Diabetes y Salud Reproductiva
Ciudad Hospitalaria «Dr. Enrique Tejera»/ Universidad de Carabobo
Valencia, Venezuela

"Las pautas internacionales para la atención de mujeres con diabetes en el embarazo permanecen fragmentadas. El desarrollo de un conjunto de pautas basadas en el consenso de la mejor práctica internacional permitiría superar muchos de los malentendidos asociados con la diabetes en el embarazo"

Cutchie et al. Diabetic. Med.2006; 23: 460-468

❑ **NIVEL DE ATENCION III: Hospitales III/IV**

- Equipo Interdisciplinario: Médico(a)s especialistas: Endocrinología/ Medicina Interna / Diabetología, Gineco-Obstetricia, Medicina Materno-fetal, Neonatología, Enfermera(o), Nutricionista, Educador(a) en Diabetes, Otros

•Interconsultas a Oftalmología, Nefrología, Cardiología

•Unidad de Cuidados Intensivos Maternos y Neonatales

❑ **ATENCION AMBULATORIA**

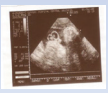
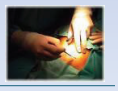
Periodicidad de las consultas: Semanal/Quincenal

❑ **HOSPITALIZACIÓN:** Deterioro del control metabólico, Infecciones sistémicas, HTA severa, Complicaciones obstétricas, Resolución del embarazo

❑ SEGUIMIENTO CLINICO-METABOLICO MATERNO

- Optimo Control Metabólico de la Diabetes
- Evaluación de Complicaciones Crónicas en Diabetes tipo 1 y 2
  - ○Retinopatia
    Evaluación oftalmológica inicial , a las 16-20 sem si hay retinopatia y a las 28 sem
  - ○ Nefropatía: Evaluación renal inicial y periódica dependiendo de los resultados
    NICE Guideline Published: 25 February 2015 nice.org.uk/guidance/ng3
- Detección y Tratamiento de Infecciones Asociadas
- Confirmación de Síndromes Hipertensivos y conducta apropiada

❑ VIGILANCIA CONTINUA DE LA SALUD FETAL

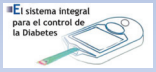



❑ ATENCION OBSTETRICA ADECUADA

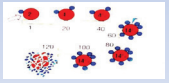
ESTRICTO CONTROL METABOLICO MATERNO

❑Perfil Glucémico

❑Cetonemia: < 0.6 mmol/l
Cetonuria: Negativa



❑Hemoglobina Glucosilada A_{1c} /
Fructosamina



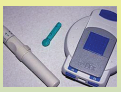
ESTRICTO CONTROL METABOLICO MATERNO

VALORES META

Org.	HbA1C (%)	Glucemia (mg/dl) Preprandial	1h post-comidas	2h post-comidas
IDF 2009	<6 (c/1-2 m)	<100	<140	<120
ES 2013	<6.5 - 7	<90-95	<140	<120
ALAD 2015	<6.5 (c 4- 6 sem)	70-90	< 140	<120
NICE 2015	<6.5 1era Consulta 2° y 3° Trimestre	<95	<140	<120

IDFGlobal Guideline on Pregnancy and Diabetes 2009
J Clin Endocrinol Metab 98: 4227–4249, 2013 / NICE Guideline Published: 25 February 2015 nice.org.uk/guidance/ng3

ESTRICTO CONTROL METABOLICO MATERNO



PERIODICIDAD

❑ Glucemias

- **DG con medidas no farmacológicas**: 4 (Ayunas y 1 hora post-comidas) 3-4 días/semana
- **DG tratada con insulina y DPG2**: 4 diarias (Ayunas y 1 hora post-comidas)
- **DGP1:** 6-7 diarias (Pre y 1 hora post-comidas. Ocasionalmente una entre 2 y 5 a.m.)

❑ **HbA1c**: c/4-6 semanas

ESTRICTO CONTROL METABOLICO MATERNO

MONITOREO CONTINUO DE GLUCOSA

Embarazadas con Diabetes tipo 1

- Hipoglucemias severas
- Inestabilidad en los valores de glucemia

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

TRATAMIENTO



•NO FARMACOLOGICO

EDUCACION GRUPAL E INDIVIDUALIZADA
NUTRICION
EJERCICIOS QUE NO CAUSEN CONTRACCIONES UTERINAS NI ESTRÉS FETAL
MANEJO ADECUADO DEL ESTRÉS
CESACION DEL TABACO


•FARMACOLOGICO

❖INSULINA ACCION CORTA:

REGULAR, ANALOGOS LISPRO Y ASPART

❖INSULINA ACCION LARGA: NPH Y DETEMIR

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

PLAN ALIMENTARIO INDIVIDUALIZADO

•CALORIAS
• 1° trimestre: 30-35 Cal/Kg p/d
2° y 3° trimestres: Agregar 300 cal/d

•PESO IDEAL	30 cal/Kg/d
20-50% PI	25 cal/Kg/d
> 50% PI	20 cal/Kg/d
< 10% PI	35-40 cal/Kg/d

•COMPOSICION

CHO *Bajo IG* : 45-55%
<40%*
PROTEINAS: 20-25%
GRASAS: 30-35%
* Riesgo RN macrosómico

· DISTRIBUCION

TRES COMIDAS Y TRES MERIENDAS

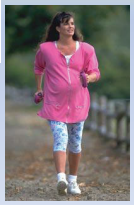
*Diabetes Care 2014;37:1254–1262

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

Ejercicios

▪Sin Presión Sobre la Mitad Inferior del Cuerpo

▪ Evitar Producir Contracciones Uterinas



▪Sin Causar Stress Fetal

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

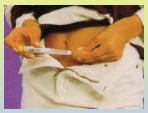
INSULINA: Uso en Embarazo

Tipo	Categoria	Investigación Seguridad
Regular y NPH	B	Múltiples trabajos
Análogos acción corta		
Aspart	B	Petit DJ. Diab. Care 2003; 26: 183 Mathiesen ER. Diab. Care 2007; 30: 771
Lispro	B	Jovanovic L. Diab Care 1999; 22: 1422 Bhattacharyya S. Diab Care 2001; 94: 255
Glulisina	C	No ha sido evaluada aún en el embarazo
Análogos acción larga		
Glargina	C	Requiere ensayos aleatorios
Detemir	B	Mathiesen E. Diab Care 2012; 35: 2012–2017

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

Insulina

❑Tipo
•Humana Regular y NPH
En la mayoría de las pacientes
NICE Guideline Published: 25 February 2015 nice.org.uk/guidance/ng3



• Análogos de acción corta: Lispro y Aspart

• Análogos de acción larga: Detemir

En pacientes con diabetes tipo 1 con tendencia a hipoglucemias

❑ Esquemas

• Basal-bolus de 3, 4 o más inyecciones/ día

• Bombas de infusión continua

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

Insulina vs Hipoglucemiantes orales

❑ En Venezuela la insulina humana es distribuida gratuitamente o adquirida a muy bajo costo

❑ Las indicaciones de Metformina

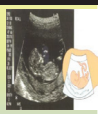
Continuarla en casos de Síndrome de Ovario Poliquístico que ya la venía recibiendo y hacen una Diabetes Gestacional

Pacientes con Diabetes Gestacional donde por alteraciones de salud mental, se considere que la insulina puede representar un riesgo muy alto

En los demás casos, así como para el uso de Glibenclamida, esperar investigaciones a más largo plazo y la aprobación de los organismos nacionales e internacionales

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

VIGILANCIA DE LA SALUD FETAL



❑ Confirmar viabilidad del embarazo entre las 7-9 semanas

❑Ecografía a la semana 20 para detectar anomalías congénitas

❑ Ecografía cada 4 semanas entre las semanas 28 y 36 para evaluar crecimiento fetal y volumen de líquido amniótico

❑ Pruebas de bienestar fetal
• Registro basal no estresante 2 veces por semana desde la semana 32

• Perfil biofísico en las últimas semanas con indicación individualizada

NICE Guideline Published: 25 February 2015 nice.org.uk/guidance/ng3

TRATAMIENTO DE LA DIABETES Y LA HIPERGLUCEMIA EN EL EMBARAZO

ATENCION OBSTETRICA ADECUADA

❑ Inducción de madurez pulmonar fetal con betametasona

•Indicada solo si hay interrupción pre-término del embarazo

•Administración simultánea de insulina regular mediante infusión intravenosa continua

❑ La diabetes per se no constituye una indicación de cesárea, aun cuando su frecuencia es alta

❑ La resolución del embarazo generalmente entre las 38-39 semanas

UNIDAD DE DIABETES Y EMBARAZO
UNIVERSIDAD DE CARABOBO
CIUDAD HOSPITALARIA "Dr. ENRIQUE TEJERA"

MUCHAS GRACIAS

VALENCIA, VENEZUELA
1986- 2015

PAN AMERICAN CONFERENCE ON DIABETES & PREGNANCY
SEPT 8|10 2015 LIMA PERU
Hotel Sol de Oro
Calle San Martín 305, Miraflores - Lima - Perú

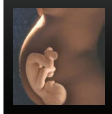
Pan American Health Organization | World Health Organization

Post-parto Seguimiento y Prevención

Educación en Diabetes Gestacional
para prevención de la Diabetes Mellitus

Prof. Silvia G de Lapertosa
Profesor Titular Nutrición y Educación para la Salud
Profesor Adjunto Medicina II
Presidente GLED
Vice Chairman DIAMU SACA IDF

¿Porque educar?



Ciclo Vicioso

MADRE

Tabaquismo
Hipertension
Obesidad morbida

Hipe...

...perglucemia
Obesidad
...de peso
Hipertrigliceridemia

Rompiendo con estrategias de prevención e intervención efectivas

Enfermedad cardiovascular

Bajo peso para edad ...acional

Macrosomia fetal

Diabetes tipo 2

HIJO

CUADRIGA DE TRATAMIENTO

Educación como herramienta terapéutica

CALIDAD DE ATENCIÓN DE PERSONAS CON DIABETES TIPO 2 EN LATINOAMÉRICA: ¿HAY EVIDENCIA DE DISPARIDAD DE GÉNERO?

E. Wandurraga1, J. Villena Chávez2, V. Stepenka3, C.L. Solís4, D. Ramirez de Peña5, F. Perez Manghi6, M.A. Padrón7, H. Manrique8, D. Lujan9, S. Lapertosa10, J. Gonzalez11, G. Fuente12, C. Faingold13, V. Commendatore14, P. Aschner9, L. González15, J. Elgart15, J. J. Gagliardino15, DIFAR Academic Committee†

- Mujeres presentaron valores significativamente mayores de IMC, obesidad y menores de presión arterial y tabaquismo.
- Los valores de HbA1c fueron similares
- Colesterol total y sus fracciones fueron mayores en mujeres.
- Monoterapia con antidiabéticos orales en mujeres y combinada en hombres.
- La terapia combinada de hipertensión fue mayor en hombres.

En países de Latinoamérica se registra, a nivel de servicios de diabetes, la existencia selectiva de indicadores clínico/metabólicos que sugieren disparidad de género en el control de personas con DMT2 y FRCV asociados. Su magnitud no se reflejaría en la frecuencia de complicaciones según género.

Revista ALAD Volumen 4 N° 3 2014

Interventions to modify the progression to type 2 diabetes mellitus in women with gestational diabetes: a systematic review of literature

Suzanna Morton[a], Samantha Kirkwood[b], and Shakila Thangaratinam[b,c]

Efecto de Intervenciones en la progresión a DM2 después de embarazo complicado con DG

(a) Randomized trials

Study year	Number of women	Intervention	Intervention group risk/estimate	Control group risk/estimate	Outcome	Effect estimate
Diet and lifestyle						
Ratner et al. [11] 2008	350	Intensive lifestyle	7.4/100 person-years	15.2/100 person-years	T2DM	RR 0.50; P=0.006[a]
Wein et al. [10] 1999	200	Diet and exercise	6.1% annual incidence	7.3% annual incidence	T2DM	RR 0.63 [95% CI 0.35–1.14] P=0.12
Shek et al. [9**] 2014	450	Diet and exercise	33/225	43/225	T2DM	RR 0.77 [95% CI 0.51–1.16]
Shyam et al. [12] 2013	77	Low-glycaemic index diet	Median 0.2 mmol/l (IQR 2.8)	Median 0.8 mmol/l (IQR 2.0)	Change in blood glucose 2h post-75g glucose load from baseline	P=0.025
Pharmacological interventions						
Buchanan et al. [12] 2002	266	Troglitazone 400mg	5.4% annual incidence	12.1% annual incidence	T2DM	HR 0.45 [95% CI 0.25–0.83] P=0.009
Ratner et al. [11] 2008	350	Metformin	7.8/100 person-years	15.2/100 person-years	T2DM	RR 0.47; P=0.002[a]
Berkowitz et al. [16] 1996	42	Troglitazone 200mg	88 ± 22[@]	4 ± 14%[@]	Insulin sensitivity[@]	P=0.03
		Troglitazone 400mg	40 ± 22[@]			

@ means ±SE calculated as 100 × [12 week − baseline]/baseline. HR, hazard ratio; IQR, interquartile range; RR, relative risk. [a]Note: confidence intervals not provided.

Interventions to modify the progression to type 2 diabetes mellitus in women with gestational diabetes: a systematic review of literature

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(b) Comparative cohort studies

Study year	Total number of women	Intervention	Intervention group risk	Control group risk	Outcome	Effect estimate
Diet and physical activity						
Bao et al. [14**] 2014	4554	Physical activity	108 /1138	221/1140	T2DM	RR 0.5 [95% CI 0.38–0.65]; P<0.001[a]
Tobias et al. [13] 2012	4413	A Med diet	7.9 per 1000 person-years	11.2 per 1000 person-years	T2DM	HR 0.84 [95% CI0.73–0.96][b]
		DASH diet	7.5 per 1000 person-years	12.1 per 1000 person-years		HR 0.86 [95% CI 0.73–1.03] P=0.1
		aHEI diet	6.9/1000 person-years	11.6/1000 person-years		HR 0.77[95% CI 0.64–0.93]
Breastfeeding						
Steube et al. [18] 2005	266	Lactation	N/A	N/A	T2DM	HR 0.96 [95% CI 0.84–1.09][b]
Ziegler et al. [19] 2012	264	Lactation	15 year risk 42% [95% CI 28.9–55.1)	15 year risk 72% [95% CI 60.5–84.7)	T2DM	HR 0.55 [95% CI 0.35–0.85) P=0.000[a]

DASH, dietary approaches to hypertension; aHEI, alternate healthy eating index; aMED, alternative Mediterranean diet.
[a]comparing most active and least active quartiles [b]for 1-unit increase in IQR [c]per additional year of lactation [d]comparing lactation for >3 months with <3 months.

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PUNTOS IMPORTANTES

- **Intervenciones en estilo de vida y dieta tienen la potencialidad de reducir la progresión a DM2 en mujeres con DG.**
- **Amamantar puede tener un efecto protector para la progresión a DM2.**
- **La efectividad y perfil de eventos adversos como MET en madres en etapa postnatal podría prevenir el desarrollo de DM2 pero requiere más estudios.**

CALIDAD DE VIDA , DESEOS Y NECESIDADES DE LAS MUJERES CON DIABETES GESTACIONAL: ESTUDIO EMBARAZO DAWN ITALIANA
A. LAPOLLA, ET AL.

PREOCUPACIONES DE LAS PACIENTES POR SU EMBARAZO (P < 0.05)

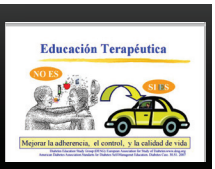
Hindawi Publishing Corporation International Journal of Endocrinology, Volume 2012, Article ID 784726, 6 pages,doi:10.1155/2012/784726

DIFICULTADES Y ANSIEDAD RELACIONADAS AL MONITOREO DIABÉTICO

DIFICULTADES EN SEGUIMIENTO	ITALIANOS	INMIGRANTES
Asesoramiento dietético (%)	58	43,5*
Monitoreo glucémico (%)	93	36,5°
Actividad física (%)	50,5	61
Incremento ansiedad por terapia insulínica (%)	31,5	40
*P < 0.02; °P > 0.01		

Hindawi Publishing Corporation International Journal of Endocrinology, Volume 2012, Article ID 784726, 6 pages,doi:10.1155/2012/784726

EDUCACIÓN TERAPÉUTICA



- Proceso continuo
- Integra el tratamiento
- Dota al paciente de conocimientos, habilidades y destrezas para lograr el control de su enfermedad.
- Lograr un cambio de conducta.
- Incluye a la familia.
- Brega por una excelencia en la atención sanitaria tendiente a una buena calidad de vida

P.Assal,2000
D.Figuerola,2009

HOSPITAL DE DIA.

- **Objetivo general:** Mejorar los resultados perinatales en las mujeres embarazadas con diabetes atendidas en la maternidad del Hospital José Ramón Vidal.
- **Objetivo específico:** Que las pacientes embarazadas con diabetes adquieran conocimientos, destrezas y actitudes para lograr una mejor calidad en el desarrollo de su embarazo y disminuir la incidencia de internaciones relacionados con el tratamiento de dicha patología.

Resultados

RIESGO CESAREA	0,61(0,23-1,63)	0,3229
INTERNACION NEO	0,77(0,27-2,18)	0,62

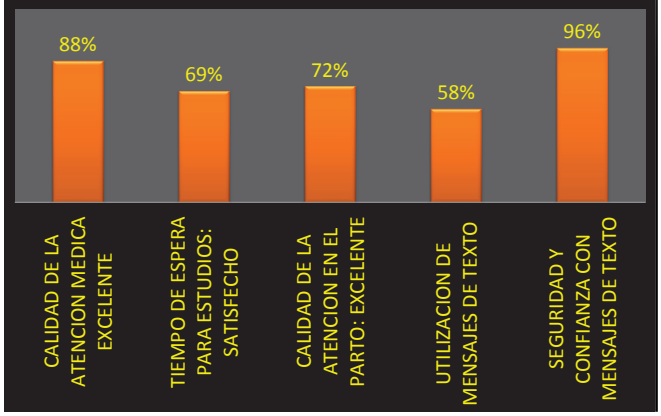
INDICADORES DE PROCESO N 43	SIN EDUCACION %-N	CON EDUCACION %-N	P
BMI	11 (5)	98 (42)	<0,000
PROTEINURIA	47(20)	93 (40)	<0,000
ECG	61 (26)	98 (42)	<0,000
FONDO DE OJO	61 (26)	98 (42)	<0,000

ESCALA DE VISUALIZACION ANALOGICA	PRE PROGRAMA EDUCATIVO X ±	POST PROGRAMA EDUCATIVO X ±	P
N 43	55,1 ± 18,3	65,7 ± 19,4	<0,000

WHO 5

WHO 5 N 43	PRE PROGRAMA EDUCATIVO %-N	POST PROGRAMA EDUCATIVO %-N
≤ 28 (Requiere tratamiento)	11,6 (5)	9,3 (4)
28-50 (> 29 - <50 Requiere PAID)	25,6 (11)	9,3 (4)
≥ 50(Sin problemas)	62,8 (27)	81,4 (35)

ENCUESTA DE SATISFACCION %



MENSAJES DE TEXTO

Buen día doctora, quería avisarle que desde el lunes me estoy aplicando la insulina. 2 antes del desayuno y 4 antes del almuerzo y cena. Los valores que me dieron fueron. Desde el viernes al domingo en ayuna 87, 81,82 y 78 hoy. Post desayuno 116,96,88,119. Post almuerzo 117,97 y 121 y post cena 121,169 y 137.

HOLA DCTRA SOY TORALE LIDIA MIS BALORE SON EN HAYUNA 93 A 100 EN HALMUERSO 100 A 88 Y CENA 130 A 113 ESTA BIEN

Buenas tardes doc. Le pasó mis controles fecha cinco.160. 105. 87.138.110. 230. Fecha seis 136. 115.110.122.130.251. Fecha siete 128.120.110.130.140.160

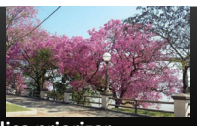
hola doc soy roxana mañana me internan para hacerme la cesarea en el hospital tengo q colocarme la insulina pre desayuno o no

Buenas tards Dra le cuento q el viernes tuve a mi bebucho y gracias a Dios todo bien peso 3,700kg.muchas gracias y nos estaremos viendo en cualquier consulta

Nace hoy doc. A las 4 de la tarde. Soy elina lopez paciente de salon. No tengo nada liquido y insuficiencia placentaria.

Dotora,como le va.?soy aliaz de bella vista.esto son los valores de los analisis, basal 0.75,120min 0.83

CONCLUSIONES



- ❖Prevenir la progresión a DM2 implica priorizar esfuerzos costo efectivos: Educación Terapéutica
- ❖Lograr un acceso apropiado a la atención
- ❖Centrada en la mujer y su grupo familiar que atienda al logro de metas de Guías Internacionales
- ❖Implementar un Programa de seguimiento y Consultorios de Nutrición en Maternidades y APS

REVIEW
THE POLYGLANDULAR AUTOIMMUNE SYNDROMES

SÍNDROMES AUTOIMUNES POLIGLANDULARES

HELEN C. PERUSSOLO ALBERTON*

Keywords: Key words: Polyglandular Autoimmune Syndromes, Addison's disease, Type 1 diabetes mellitus
Descritores: Sindromes poliglandulares autoimmunes, Doença de Addison, Diabetes tipo1

Abstract

Polyglandular Autoimmune Syndromes (APS) encompasse several conditions conditions in which there is coexistence of two or more autoimmune endocrine disorders organ-specifics. APS 1 is defined by mucocutaneous candidiasis, hypoparathyroidism and Addison's disease, while APS type 2 is characterized by Addison's disease plus type 1 diabetes mellitus and/or chronic thyroiditis. Presently we revise definitions, associated diseases, pathophysiological and genetic aspects. **Endocrinol diabetes clin exp 2015 1808 -1812.**

Resumo

As síndromes poliglandulares autoimmunes (SPA) representam um grupo de condições nas quais coexistem duas ou mais desordens auto-imunes órgão específicas. SPA1 é diagnosticada pela associação de candidíase mucocutânea, hipoparatiroidismo e doença de Addison. SPA2 é caracterizada por doença de Addison, diabetes tipo1 e/ou tireoidite crônica. Presentemente serão revisadas a definição da síndrome, doenças associadas e aspectos genéticos e fisiopatológicos da mesma. **Endocrinol diabetes clin exp 2015 1808 -1812.**

DEFINITION AND EPIDEMIOLOGY

The Polyglandular Autoimmune Syndromes (PAS) comprise a spectrum of autoimmune disorders characterized by the simultaneous presence of at least two endocrine autoimmune diseases. PAS is divided into several forms. A rare juvenile form with an increased prevalence in certain populations (people of Finland and Iranian Jews) is recognized as type 1 PAS (1,2). Type 2, the more common adult type, includes adrenal insufficiency. In type 3, it is found autoimmune thyroid deficiency and this form can be subdivided in 3A - associated with diabetes mellitus (DM)-1; 3B- associated with pernicious anemia and 3C - found with vitiligo and/or alopecia or other autoimmune disease. Type 3 PAS is often observed in individuals from same family, with a greater prevalence among women (3). PAS 4 refers to association of two or more organ-specific autoimmune diseases (1,2). (Table 1)

TABLE 1: PAS Classification - Adapted from Neufeld M, Blizzard RM (1980) (6).

Type 1 PAS	*At least two present: Chronic Candidiasis, Chronic Hypoparathyroidism, Addison's Disease*
Type 2 PAS	*Addison's Disease (always present), Thyroid Autoimmune Disease and/or Type 1Ddiabetes*
Type 3 PAS	*Thyroid Autoimmune Disease associated with other Endocrine Autoimmune Disease (excluding Addison's disease and/or Hypoparathyroidism)*
Type 4 PAS	*Combination of organ-specific autoimmune diseases not included in the previous groups.*

The PAS type 1 usually appears in infants and children at age 1-3 years or even in adolescence and it is best defined by a persistent fungal infection (chronic mucocutaneous candidiasis), associated with acquired hypoparathyroidism and Addison's disease. (Figure 1) (1,2,4-10)

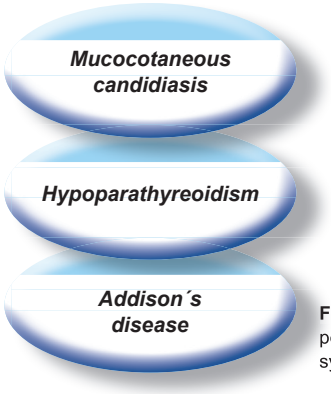


Figure 1: Components of polyglandular autoimmune syndrome (PAS) type 1

The mucocutaneous candidiasis precedes the other autoimmune association in most of the cases and it has been found more frequently in populations with a high degree of consanguinity. This form is very rare in general population. (9)

The PAS type 2 has a greater prevalence, estimated around 1:20.000 and it is more frequent in women, between 20-60 years of age. It has a strong familiar component and it is best characterized by the presence of Addison's disease, DM-1 and chronic thyroiditis. (Figure 2) (1,2).

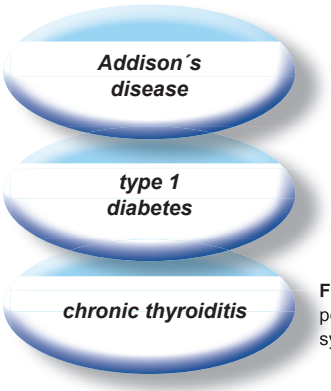


Figure 2: Components of polyglandular autoimmune syndrome (PAS) type 2

The coexistence of autoimmune adrenal insufficiency and chronic thyroiditis is known as Schmidt's Syndrome (5). The complete form involving the three organs (adrenal, pancreas and thyroid) was first described in 1931 and later on in postmortem studies showing that some Langerhans islets had lymphocytic infiltrations similar to that found in adrenal and thyroid glands. Such finding indicates a common autoimmune process underlying the involvement of these three glands.(3,4,6). The complete triad can be also named Carpenter's Syndrome (or Schmidt's Syndrome with autoimmune diabetes mellitus) (5,6).

In table 2 there are the comparison between PAS1 and PAS2.

*Department of Internal Medicine of Santa Casa de Misericórdia de Curitiba –PR-Brazil
E-mail: helenperussolo@hotmail.com

	PAS type 1	*PAS type 2*
Prevalence/incidence	*Very rare/ <1:100000/year*	*Relatively common/ 1-2/10000/year*
Male : female	*3:4*	*1:3*
Onset	*Childhood*	*Childhood through adulthood*
Inheritance	*Monogenic – AIRE gene*	*Polygenic*
HLA genotype	*Diabetes (risk decreased with HLA-DQ 6)*	HLA-DQ2 and HLA-DQ8; HLA-DRB1*0404
Autoimmune endocrine diseases	*Hypoparathyreoidism (80-85%) + Addison's disease (60-70% + Type 1 diabetes (<20%) + Hypogonadism (12%) + Thyroid disease (10%)*	*Thyroid disease (70-75%) + Type 1 diabetes (50-60%) + Addison's disease (40%) + Hypoparathyroidism (3%) + Hypopituitarism (0-2%)*
Concomitant disease	*Mucocutaneous candidiasis (70-60%)*	*No candidiasis*
Non-endocrine associated diseases	*Immune gastritis, pernicious anemia, celiac disease, immune hepatitis, vitiligo, alopecia, lupus, myasthenia gravis, rheumatoid arthritis, Sjögren's syndrome*	

Table 2: Comparative Table PAS Type 1 vs. Type 2 – Adapted from G J Kahaly (4)

PATHOGENESIS

The autoimmune component

Autoimmune diseases are clinical syndrome due to activation of T cells or B cells, or both, in the absence of infection or other discernible cause (1). The majority of immune diseases are caused by generalized defects in lymphocyte selection, regulation or by aberrant responses to particular antigens. The genetic susceptibility, environmental antigens, internal triggers of auto reactivity are contributors to mechanism of auto immunity (11). Recently, many enzymes, hormones and receptors have been identified as target auto-antigens in organ-specific autoimmune diseases (1,2). Similarly, cell-mediated immune mechanisms play a role in the immunopathogenesis of PAS and the main finding is loss of immunologic tolerance to a peptide within a specific molecule of the target organ (1,10,12). Distinct HLA alleles contribute to disease by determining which peptides are targeted and consequently which tissue will be affected (13).

When an antigen is recognized by a naive CD4 T cells causes its differentiation in effector Th1, Th2, Th 17 and Treg cells that produces specific cytokines (2,10,14). Th1 cells produce IFN gamma and TNF alpha and may regulate antigen presentation and immunity against intracellular pathogens, while Th2 cells produce interleukin IL-4, IL-5, and IL-13 and mediate humoral responses and immunity against parasites. Th2 cells are also important mediators of allergic diseases (13). Th17 are cells that express IL-17, IL-21 and IL-22 and participate in inflammation and autoimmunity processes (7,11,13). Recent studies have suggested that auto antibodies to Th17 cell cytokines IL-17A, IL-17F, and IL-22 appear in APS1 subjects and may explain their increased susceptibility to *candida* infections (2).

The regulatory cells (Tregs cells) which are implicated in the equilibrium between self-tolerance and autoimmunity express forkhead box P3 (Foxp3) transcription factor and secret transforming TGF-β and IL-10. Depletion of Tregs causes autoimmunity in mice and dysfunction of Tregs has been linked to autoimmune diseases. Defects of suppressive function of Tregs may contribute to uncontrolled expansion of auto aggressive lymphocytes (1,2,5,10)

PAS I results from a Th2 immune response to autoantigens with a defect in protective Th1 responses against invasion of *Candida albicans*. A person genetically predisposed would be at risk of developing an autoimmune process after infection, by a mechanism of cross-reactivity or by a Th2-dependent immune process of humoral origin.

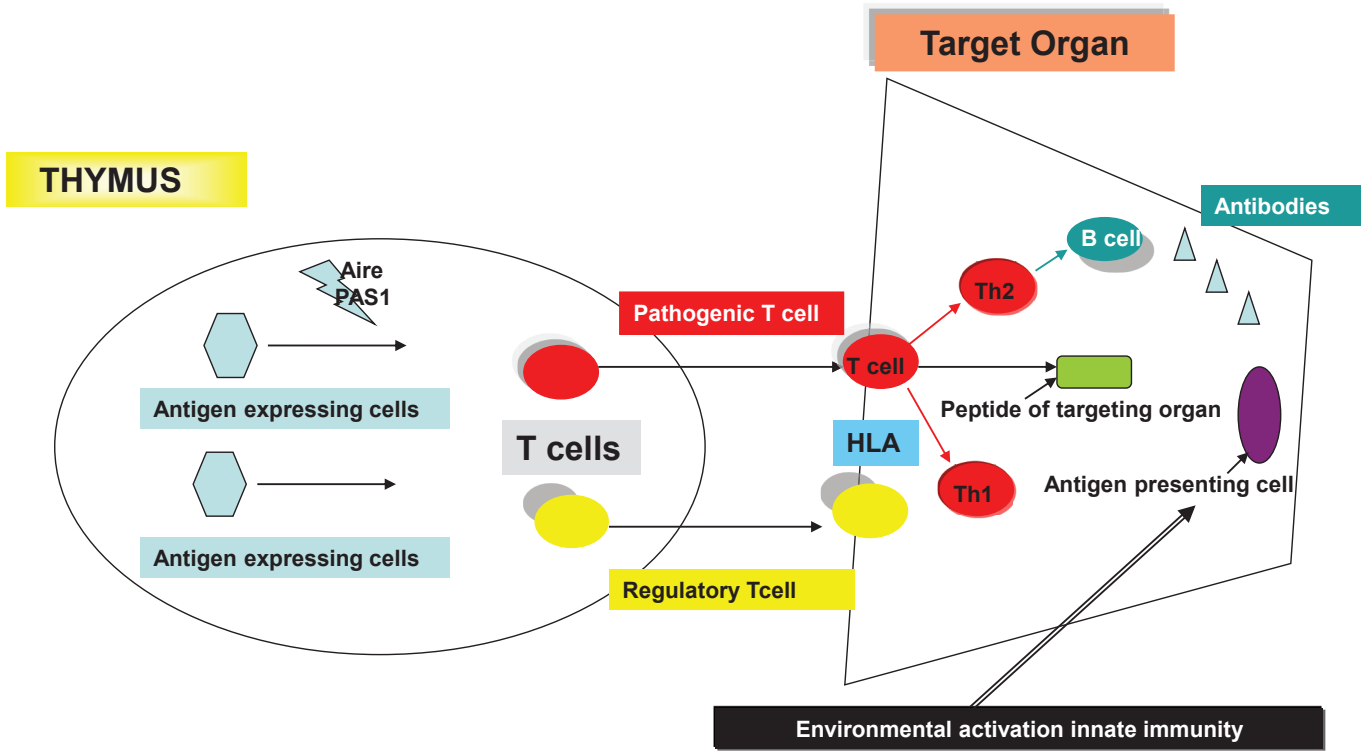


Figure 3 -Pathogenic Model of Autoimmune Polyendocrine Syndrome Disorders

A subgroup of T cells that recognize one or more peptides of target organ determines the auto immune disease. These peptides when bound to HLA molecules are presented to the T-cell receptor (TCR) of T lymphocytes. Then B lymphocytes stimulated by T cells produce autoantibodies.
There are expression of peripheral antigens of target organs in the thymus. These cells influence the balance between regulatory and pathogenic T cells. Innate immunity relates to the second signals, activates T lymphocytes by antigen-presenting cells (adapted from Eisenbarth et al 2004)

Another important aspect in the mechanisms of autoimmune diseases is related to the activity of the enzyme deoxyribonuclease-1, a tissue glycoprotein important in the regulation of apoptosis. It catalyses DNA hydrolysis and it deficiency may result in reduced or delayed removal of DNA from nuclear antigens promoting its exposition to autoimmune system and creating susceptibility to autoimmune diseases. The activity of this enzyme is lowered in PAS1 (1,2,11)

Antigen complexes containing DNA can initiate the autoimmunity disease by stimulation of the toll-like receptors (TLRs) from innate immune.TLRs receptors are found in macrophages, B cells and dendritic and responsible for recognition of molecular structures found in most micro-organisms.

Decreased serum DNase activity with elevated levels of circulating DNA and activation of TLRs immune stimulating pathway could be associated to the process of autoimmune diseases (15).

Genetics and PAS

PAS type 1 is a form of monogenic disease with an autossomal recessive inheritance, being the mutation in AIRE (*autoimmune regulator*) gene, located in chromosome 21q22.3 an important factor. This specific gene is present in tissues related with the immune maturation as lymph nodes, peripheral blood cells and mainly in epithelial antigen-presenting cells in the thymus, where it is involved in induction of self-tolerance, by driving the transcription of a great variety of tissue-specific antigens. The *AIRE* gene is known as an important immune mediator since it regulates negative selection of organ-specific T-cells. The presence of mutated *AIRE* gene will result in defective synthesis of proteins which cause autoimmune destruction of target organs by broking the immunologic tolerance.(1,2,10) Mutations in the *AIRE* gene presence of associated HLA class II alleles such as DR3 may cause many autoimmune diseases including type 1 diabetes, hypothyroidism, pernicious anemia, alopecia, vitiligo, hepatitis, ovarian atrophy, and keratitis. Some patients have diarrhea or obstipation that may be related to the destruction of gastrointestinal endocrine cells (enterochromaffin and enterochromaffin-like cells) (16).

In PAS type 2 there is a complex interaction of inheritance factors, with genes in chromosome 6 playing a predominant effect. In humans this chromosome contains the MHC loci and in some families, autoimmune endocrine syndromes susceptibility seems to be inherited as an autosomal dominant form associated with a specific HLA haplotype. However despite that the genetic factor is directly related with disease's occurrence, the concordance in monozygotic twins is less than 100%, suggesting that environmental triggers such as viral or bacterial infections and psychosocial factors may be involved in disease pathogenesis. Additionally, a polymorphism of the cytotoxic T lymphocyte antigen 4 (CTLA-4) gene was found to be associated with Addison's disease in PAS 2 in English patients (7). Thus, PAS 2 is probably a polygenic disease with autosomal dominant inheritance and incomplete penetrance. There is an association of the PAS 2 component diseases with HLA alleles B8 and DR3. The genotype DR3/4, DQ2/DQ8 with DRB1*0404 has been found to be the highest HLA genotype risk for Addison's disease, either as a single disease or within PAS 2 and HLA DR3 was identified in association with Hashimoto's thyroiditis (1,2,10).

There is evidence that MHC class III genes are associated with PAS 2, specifically the gene encoding TNF-alpha, a proinflammatory cytokine, which mediates inflammatory and immune functions. TNF-alpha mobilizes immune cells as well as induces aberrant expression of MHC class II antigens. As a consequence, an increased expression of TNF-alpha might cause inflammation and tissue damage (17,18).

CLINICAL FEATURES AND SCREENING

Autoimmune polyendocrine syndrome type 1 may be a severe disease that often appear early in life. Typically affects

infants with persistent candida infections in skin and mucous membranes and generally associated with severe immunodeficiency. The diagnosis is usually late, with hypocalcemia due to hypoparathyroidism or Addison's disease. The presence of mutations in the AIRE gene causes many autoimmune diseases, and affected patients are at risk for the development of multiple additional autoimmune diseases associated like type 1 diabetes, hypothyroidism, pernicious anemia, alopecia, vitiligo, hepatitis, keratitis and ovarian insufficiency (1,2). In most cases of PAS 1, candidiasis is the first manifestation , appears before 5 years of age and usually affects nails, skin, tongue and mucous membranes, but it may spread to esophagus. The diagnosis is based on the clinical signs and symptoms, growth of *Candida albicans* in culture and rapid resolution during therapy. Recurrent infection and oral cancer may develop if candidiasis is not treated aggressively (1).

Hypoparathyroidism frequently appears in these patients before age of 10, presenting with hypocalcemia, hypophosphatemia and PTH normal or low. Adrenal insufficiency often presents as the third disorder, usually before 15 years of age, with high levels of ACTH, low cortisol, high renin, low aldosterone, hyponatremia and hyperkalemia (1,8,9),

The autoimmune polyendocrine syndrome type 2 is much more common and clinically more varied than type I. It occurs in adulthood during the third and fourth decades. Clinical and laboratory findings in PAS usually are similar from those when the endocrine diseases occur isolated. The onset is insidious until a symptomatic hypotension episode occurs (a classic presentation of adrenal insufficiency). It can be associated with a decreased level of the insulin dose in a patient with type 1 diabetes. These patients may have hyperpigmentation and vitiligo as well as a several-year history of intermittent and severe hypoglycemia and fatigue (1,2). Other autoimmune disorders can be present (chronic atrophic gastritis, vitiligo, hypogonadism), but less frequently if compared with PAS type 1(5). Approximately 1.5% of diabetics type 1 have adrenal

TSH, FSH, LH, free T4, testosterone, estradiol, fasting morning cortisol (<3mcg/dl), glucose, serum Na+, K+ and Ca++, blood cell count, C-peptide level, renin (increased) aldosterone (impaired).
Optional: *ACTH stimulation test; genetic screening:molecular analysis of AIRE gene, HLA typing.*

Table 3: Screening functional markers to autoimmune diseases in PAS

Organ-specific autoantibodies	**Autoimmune Disease**
Anti-21 hydroxylase; anti-25 hydroxylase antibodies,	**Addison's Disease**
Anti-thyroid peroxidase antibody; anti- TSH receptor antibodies	**Autoimmune thyroid Disease**
Anti-glutamic acid decarboxylase; anti-islet cells, anti-insulin antibodies, IA2 and ZnT8	**Type 1 DM**
Anti-tissue transglutaminase antibodies; anti-endomysial antibodies; anti-gliadin antibodies	**Celiac Disease**
Anti-parietal cell and anti-intrinsic factors antibodies	**Pernicious Anemia**
Calcium sensing receptor antibody	**Hypoparathyroidism**
Anti-17-OH	**Hypogonadism**
Anti-cytochrome enzymes	**Autoimmune hepatitis**
Anti-Tyrosine hydroxylase	**Alopecia areata**
Anti-Tyrosinase	**Vitiligo**
Anti-acetylcholine receptor	**Myasthenia gravis**

Table 4: Screening for autoimmune disease by their autoantibodies

OTHER POLYENDOCRINE AND AUTOIMMUNE SYNDROMES

X-Linked Polyendocrinopathy, diarrhea and immune dysfunction:

Rare and fatal disorder that appears in neonates with fulminant, autoimmunity and type 1 diabetes. This disease is also called XLAAD (X-linked autoimmunity and allergic dysregulation) and IPEX (immune dysfunction, polyendocrinopathy, and enteropathy, X-linked). Early diagnosis of disease is imperative since there is evidence that bone marrow transplantation, may reverse it. The disease is due to mutation in gene Scurfin or FOXP3, these genes are important in control the development of regulatory CD4+CD25+ T cells essential for the maintenance of tolerance (20,21).

POEMS syndrome (plasmacytoma):

It is characterized for the presence of polyneuropathy, organomegaly, endocrinopathy, serum M protein, skin changes (22).

Hirata's disease:

Associated to HLA-DRB1*0406 plus methimazol use during treatment of Graves' disease. This disease was described for the first time in a Japanese patient with insulin autoantibodies and hypoglycemia (23).

Type B insulin resistance:

Characterized by Insulin-receptor autoantibodies, systemic lupus erythematosus, diabetes mellitus with hypoglycemia and

hyperglycemia (1).

Thymoma:

It has with red-cell aplasia, myasthenia gravis and Graves' disease. Early diagnosis of these diseases is important to start specific therapy (1).

TREATMENT

Many of the endocrine disorders of PAS are adequately treated with hormonal replacement therapy especially if the diagnosis is early, but it is essential to consider the presence of interferences between diseases and each one therapy and their correlated management. In example, hypoglycemic episodes and decreasing insulin requirement in a type 1 diabetic patient can be a sign of an initial adrenal failure. Besides, in patients with suspected concomitant Addison's disease and hypothyroidism, thyroid replacement should not precede the glucocorticoid replacement, since thyroid replacement may precipitate the adrenal crisis due to the action of thyroxine in increasing hepatic corticosteroid metabolism. Removal of gluten from the diet is the treatment for celiac disease (1,2,3,4,5).

In PAS-1, the treatment includes an aggressive eradication of candidiasis, antibiotic prophylaxis if asplenism is present and tests for early detection of hepatitis.

CONCLUSION

The imbalance between autoimmune effector and regulatory T lymphocytes is the major determinant of auto immune diseases such as PAS; HLA alleles determine specific tissue targeting.

The clinician recognition and early detection of PAS may be life-saving for some patients. Researches with focus in the tolerance restoration may bring new tools to improve quality of life for all patients with this syndrome.

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CASE REPORTS
VON GIERKE DISEASE: CASE REPORT AND LITERATURE REVIEW

DOENÇA DE VON GIERKE: RELATO DE CASO E REVISÃO DA LITERATURA

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Descritores: Glicogenose, Glicose, von Gierke

Abstract

Glucose, a monosaccharide carbohydrate, is highly relevant in the human body, providing energy throughout many metabolic pathways. It can be obtained by food intake or generated through glycogenolysis or gluconeogenesis. The Von Gierke disease or Glycogen Type Ia, is an autosomal recessive disorder in which the catalytic unit responsible for dephosphorylation of the glucose-6-phosphate is deficient, preventing the glucose breakdown. This disease usually begins its manifestation with hypoglycemia, moreover, hepatomegaly is usually present due to the massive deposition of lipid and glycogen in the liver. The symptoms can also be started with the appearance of recurrent infections and concurrently there is a wide spectrum of metabolic manifestations. The diagnosis is performed through genetic studies associated with clinic and biochemical data of the patient. The liver biopsy is reserved for inconclusive cases in which genetic tests cannot be performed. The main stage of the treatment of these patients consists of a strict nutritional therapy combined with drug therapy aimed at regulating the metabolic profile. **Endocrinol diabetes clin exp 2015 1813 -1817.**

Resumo

A glicose, um carboidrato monossacarídeo, apresenta grande relevância no organismo humano, devido suas funções de fornecer energia e por ser o intermediário metabólico em muitas vias. Pode ser obtida através da ingestão alimentar, glicogenólise ou neoglicogênese. A Doença de Von Gierke ou Glicogenose tipo Ia, é de herança autossômica recessiva e consiste em uma deficiência da unidade catalítica responsável por desfosforilar a glicose-6-fosfato, impedindo, desta maneira, a metabolização da glicose. Esta patologia, geralmente, inicia sua manifestação através de sintomas decorrentes da hipoglicemia, além disso, hepatomegalia costuma estar presente devido o acentuado depósito de lipídeos e glicogênio no fígado. O quadro também pode ser iniciado com o aparecimento de infecções recorrentes e concomitantemente existe um amplo espectro de manifestações metabólicas. O diagnóstico da doença é realizado através de estudo genético, associado a clínica e bioquímica dos pacientes. A biópsia hepática é reservada para casos inconclusivos ou nos quais a pesquisa genética não pode ser realizada. A principal etapa do tratamento desses paciente consiste em uma terapia nutricional rigorosa associada à terapia medicamentosa visando regulação do perfil metabólico. **Endocrinol diabetes clin exp 2015 1813 -1817.**

INTRODUCTION

Glucose is an essential nutrient for the body and it is the primary fuel for the cells of the human body. It can be achieved primarily by diet, by the degradation of glycogen (glycogenolysis) or by production from aglicans compounds (gluconeogenesis). In the absence of nutrition, glycogenolysis is the initial responsible for maintaining blood glucose within proper levels (1).

The lack of activity of one or more specific enzymes as well as defects in the transport of protein can affect cellular metabolism and therefore they form a group of diseases called metabolic diseases. The glycogenosis are diseases resulting from a metabolic error. It is due to an abnormality of the concentration and/or the glycogen structure in any tissue of the body (2). They are classified into twelve types, according to the specific enzyme deficiency, organic tissues with change in concentration or structural defect of glycogen (3).

Glycogenosis type I accounts for 25% of glycogen storage disease cases and it is characterized by a deficiency of glucose-6-phosphatase (G-6-Pase). It is subdivided into four types: Glycogen storage disease type Ia, Ib, Ic and Id. Glycogen storage disease type Ia, an autosomal recessive inheritance, involves liver, kidneys and intestines. It results from loss of the catalytic unit responsible for dephosphorylation of the glucose 6-phosphate. Such an entity receives the eponymous von Gierke disease in honor of its discoverer Edgar von Gierke in 1929 (2,3). The disease is described in the first 28 days of life (neonatal period) when babies often present hypoglycemia after short periods of fasting or infection (3,4).

Next, it is reported the case of a patient with glycogen storage disease type I, emphasizing her clinical condition and treatment and stressing the importance of early diagnosis of metabolic diseases despite being often late discovered.

OBJECTIVE

To report a case of glycogen storage disease type Ia or von Gierke's disease in order to discuss its clinical features, diagnosis and the current available treatment

METHODOLOGY

Review of medical files and selection of scientific articles of the Bireme, PubMed, Lilacs database emphasizing the latest articles.

CASE REPORT

P.M.M., female, caucasian, 14 years and 9 months old, daughter of first cousins degree of consanguinity parents ,

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born in São Paulo (SP), living in Curitiba (PR), under outpatient follow-up at Hospital Pequeno Príncipe for inborn errors of metabolism from the age of 8 months.

The mother was the informant. She told that from birth the child had experienced several episodes of severe hypoglycemia and repeated infections. At 2 months she was admitted to the Intensive Care Unit at Santa Casa de São Paulo, due to a non-specified vaccine reaction. At the time, the hospitalization was extended for another 3 months due to the important finding of hepatomegaly on physical examination, which culminated in a liver biopsy revealing the diagnosis, as early as 5 months of age, of Glycogen Type Ia Storage Disease, also called von Gierke's disease.

She was referred to Hospital Pequeno Príncipe at 8 months of age for multidisciplinary follow-up, where outpatient follow-up was initiated in pediatric endocrinology among other specialties (nephrology, otorrinolaringology, pulmonology, neurology, inborn errors of metabolism, orthopedics, ophthalmology and cardiology).

Her medical history revealed previous history of recurrent infectious episodes. At the age of 8 months, a tonsillectomy was performed and at the age of 1 year a surgery for scoliosis correction. She presented several episodes of diarrhea, influenza and pneumonia, which persisted until the age of 6 when such episodes were gradually becoming more infrequent. When she reached puberty, at 12 years old, a gastrostomy was carried out, in which an infusion of lactose-free milk at night was performed, seeking improvement on the glycemic control. Her menarche was at 14 years and 6 months. She is in the ninth year of school and relates learning difficulties.

Her obstetric history was unremarkable, being her mother´s only pregnancy. She was vaginally born at week 40th; with 2045g of weight and remained hospitalized for 17 days due to a meconium aspiration condition.

She had normal psychomotor development: sat at five months, walked at 12 months and first words spoken at 13 months. The vaccination calendar was always up to date. Her diet has abolished beet, carrots, fruits, fats and lactose. She has been followed up by an endocrinology pediatrician for short stature and her only complaint is chronic irritability.

Physical examination is presented in good general condition, ruddy, hydrated, acyanotic and anicteric. Weight is 35kg and height 137cm, which places her to the percentile 5. Furthermore, hepatomegaly that goes beyond 4cm in the right costal margin.

Control laboratory tests (02/16/2015):

Eritrogram		**Leucogram**	
Erythrocytes	4.35 10^6/mm^3	Leukocyte	10900 /mm^3
Hb	11,9 g/dL	Neutrophils	31%
Hematocrit	36,1%	Band	0%
VCM	83 fl	Segmented	31%
HCM	27.4 pg	Lymphocytes	57%
CHCM	33 g/dl	Atypical lymphocytes	1%
RDW	13,1%	Monocytes	11%
		Platelets	308.000 mil/mm^3

Serum		Urine 24h		Blood gas analysis	
Glucose	70 mg/dl	Volume	1000ml	pH	7,352
Triglycerides	747 mg/dl	Density	1025	pO_2	23,2 mmHg
LDL	*	Uric Ac	412 mg	sat O_2	36,1%
HDL	3,7 mg/dl	Calcium	81 mg	pCo_2	42,3%
Uric Ac	5,5 mg/dl	Creatinine	0.57 g	HCO_3	23 mg/dl
Calcium	10,2 mg/dl	Phosphorus	0.54 g	BE	-2,5
Cholesterol	248 mg/dl	Glycosuria	100 mg	CO_2T	24 mmHg
Creatinine	0,5 mg/dl	Potassium	46.8mmol		
Urea	31 mg/dl	Sodium	81 mmol		
Potassium	3,7 mEq/l	Protein	50 mg		
Sodium	139 mg/dl				
Thyroxine T4	6.6 µUI/dl				
Free T4	0.85 ng/dl				

*LDL damaged by hypertriglyceridemia

DISCUSSION

Type Ia glycogen storage disease, also known as Von Gierke's disease is a rare genetic disease (5). Its incidence in the world live birth population is around 1/100000 (3). Glycogen--storage disease Ia and Ib are autosomal recessive genetic traits caused by mutations at loci 17q21 and 11q23, respectively (5,6).

Glycogen-storage disease Ia is caused by deficient activity of the enzyme glucose-6-phosphatase and Glycogen-storage disease Ib is caused by deficiency of glucose-6-phosphate translocase. This enzyme is responsible for importing glucose-6--phosphate from the cytosol to the interior of the microsome (5,6,7). With the deficiency of this enzyme the liver loses its capacity as a glucose-homeostatic organ due to an inability to release free glucose (7,8). Studies show that microsomal transport of glucose-6-phosphate has a role in antioxidant protection of the neutrophil. A defect in this mechanism causes neutropenia and diminishing the patient's resistance to infection. Children with glycogen-storage disease Ib are susceptible to gram-positive infections more than Ia (9,10). The subtypes Ia and Ib glycogen storage disease is one of the few genetic causes of hypoglycemia in newborns (6). Many are the adaptative manners our body can respond to this life threatning unbalance. Hypoglycemia stimulates epinephrine secretion, which activates lipoprotein lipase and the release of free fatty acids from adipose tissues (2,6).

In the liver these fatty acids are assembled and exported as very-low-density lipoprotein (VLDL) causing a transient hypertrigliceridemia that will support, briefly, the cell energy input. Within the glycogen-storage disease ketosis does not develop because of the abundance of acetyl coenzyme A (CoA) derived from glycolysis which activates the acetyl CoA carboxylase enzyme that yields malonyl CoA. Since Malonyl CoA inhibits fatty acid transportation into the mitochondrion, the beta-oxidation of fatty acids to support the hypoglycemic episodes does not occur. Normally the liver clears the blood of the lactic acid, which has been produced by muscles and other tissues with a high rate of glycolysis and converts it into glucose by the usual pathways of gluconeogenesis. In type I glycogen storage disease the liver itself produces large amounts of lactic acid from glycogen, because when glycogenolysis is stimulated, the glucose 6-phosphate is diverted into the glycolytic pathway; the liver thus accentuates an existing lactic acidosis and further disturbs the acid-base balance of the body(6,7,8).

The clinical features of these metabolic errors in the first hours after birth are: irritability, apathy, hypotonia, hypothermia, seizures, cyanosis, and apnea. In older children, repeated episodes of hypoglycemia may also result in brain damage (2,3,5,6). They may present: lethargy, tremors, poor growth, increase in abdominal girth and a doll-like facial appearance caused by adipose tissue deposition in the cheeks. Liver glycogen accumulation causes hepatomegaly (6). Some newborns are healthy at birth, others are born with an enlarged, although uniform, liver. Splenomegaly does not accur. Later in life short stature with rachitics characteristics and gingivitis may also develop. Xanthoma may be found on the elbows and knees. Proteinuria with enlarged kidneys, diarrhea and recurrent infections can also be detected (7,8,9).

Laboratory findings include: persistent metabolic acidosis, hyperuricemia, hyperlactatemia, hypertriglyceridemia, hyperlipidemia, neutropenia and platelet disorders. not reach the normal serum values (6,11,12). The mentioned dyslipidemic disorders are due to the heightened uptake of lipid metabolites as to meet

energetic demands, this profile suggests that patients should present high risk to coronary disease, however; there is no report of early ischemic heart disease in these patients (6,11).

This girl, described above, as expected, presented several hypoglycemias, with documented blood glucose measurements below 60 mg/dl. In addition, total cholesterol and triglyceride measurements that exceeded the normal threshold were also found. Calderaro et als (13) described that the liver enlargement is due to fat deposition, since glycogen excess is driven to a biochemical transformation that also causes hepatocyte inflammation. The amount of bicarbonate, which now remains within normal values, came to meet 17.2 mEq/L at the initial phase of the disease, indicating metabolic acidosis. Abnormal values of uric acid were also observed, thus requiring interdisciplinary follow up (6,7).

In the case of the reported patient, the hypoglycemic crisis and the frequent need to be hospitalized to treat infections, most of them with concomitant neutropenia, were the clues to the diagnostic (9,10,11,12). It is of noteworthy that the neutropenia- infeccion state is commonly found in glycogen storage disease type Ib, however, this patient was diagnosed with the glycogen storage disease type Ia. This issue remains open. The recurrent infections are related to a neutrophilic dysfunction due to enzymatic abnormalities. They often caused by staphylococci and some Gram negative bacteria as E. *coli* and *Pseudomonas aeruginosa*, and most of them start within the first year of life. Changes in neutrophils seem to be independent of the metabolic control, requiring other approaches to the control of infections (3). The continued prophylactic use of sulfamethoxazole and trimethoprim, combined to antimicrobial during acute infection process (4) was the first approach used however, it has been proved to be of short efficacy in the present case (3).

For reasons yet to be understood, glycogenosis type Ia has a better prognosis than type Ib.

Picture 1 - Von Gierke disease* A – Poor growth, B- Lordose
• Authorized image by TCLE

The genetic diagnosis of the disease can be made with leucoyte analysis searching for the classical mutations. Biallelic mutations in *G6PC* (Ia) cause 80% of disease and biallelic mutations in *SLC37A4* (Ib) cause 20%. (14,15) A liver biopsy is reserved for inconclusive cases or when genetic tests cannot be performed. It is possible to make a prenatal diagnosis, through a DNA study (15).

TREATMENT

The treatment of von Gierke disease is based on a special diet, to ensure an optimal control of the blood glucose and a proper nitrogen balance.

• Small frequent meals and snacks high in complex carbohydrates with additional snacks throughout the day and before bedtime are recommended to maintain normoglicemia (16).

• A Night time intra gastric continuous glucose infusion through a nasogastric tube or a gastrostomy tube is also an option. Infusion with 8-10 mg/kg/min glucose for infants and 6-8 mg/kg/min glucose for older children are preconized. (16).

• Uncooked cornstarch can be offered to toddlers, orally, between meals or before bedtime. The portions of the cornstarch offered should be around 1.6 g/kg of body weight every four hours for infants, 1.7-2.5 g/kg body weight every six hours for young children through puberty, and 1.7-2.5 g/kg body weight given before bed time for adults (16).

Nutrition for growth and development:

Complex carbohydrates 60%-70% of recommended total energy intake, cornstarch and starches from whole-grain bread, rice, and potatoes for children and adolescents and rice cereals for infants. Sugar, fruits, fruit juice, high-fructose corn syrup, sorbitol, cane juice, and other foods that cannot be broken down into glucose are restricted for these patients. Lactose and galactose should be limited (1 cup of yogurt or 1 cup of milk) (17).

Protein 10% -15% of recommended total energy intake like soy formula (17).

Fat 10%-15% of recommended total energy intake as part of a low-fat diet such as canola oil and olive oil (17).

Calcium and vitamin D supplements to support bone growth and mineralization, calcium citrate or calcium carbonate with vitamin D is recommended (17).

Iron supplements to avoid anemia and iron deficiency (17).

Drug therapy

Inhibitors of angiotensin converting enzyme (ACE), targeting a renal protection, the administration of allopurinol when hyperuricemia occurs, and bicarbonate in the presence of acidosis at the expense of HCO3- below 18mEq/L, besides

vitamin supplements are indicated (3,16,17). The dyslipidemia is managed with sinvastatin or fibrate, or both (2,6). Citrate supplementation may help prevent or ameliorate nephrocalcinosis and the development of urinary calculi in dose of 1 mEq/kg/day in liquid form divided into three doses (17).Our reported patient is on sinvastatin for lipid control and under a nephrologist recommendation, alupurinol and bicarbonate were initiated. Ferrous sulfate and folic acid medications also take part of her daily routine medication (6,17).

Kidney transplantation may be required to treat severe renal insufficiency (18). When the adequate diet does not stabilize the disease or when there are signs of malignancy or an unresectable tumor in the liver, a liver transplantation is considered(19). Althought a metabolic stabilization is achieved, neutropenia may be persistent. Currently there are already therapies with stimulating factors of granulocyte colony, which restore myeloid functions, such as the increase of neutrophils, decreasing the incidence of infections (3,9). From the second or third decade of life, 50-70% of patients develop hepatic adenomas that can lead to bleeding and malignancy (20).

The proposed treatment targets a clinical improvement of the patient with life expectancy surpassing the third decade (2). Future treatment prospects aim at blood infusion of adenovirus containing human glucose-6-phosphate translocase, which would correct the metabolic and myeloid defects in this disease (3).

CONCLUSION

The diagnosis of glycogen storage disease should always be contemplated when facing intermittent hypoglycemia and/or recurrent infections in childhood. Because no specific treatment is available, symptomatic therapy is very important. The common treatment for type I glycogen storage disease is to maintain normal blood glucose concentration with adequate nutritional intervention and the pharmacological treatment of the co- morbidities.

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TOPICS IN MEDICAL CLINIC
CASE REPORT
CAMPTODACTYLY – COXA VARA SYNDROME OR JUVENILE IDIOPATHIC ARTHRITIS?

SÍNDROME DA CAMPTODACTILIA COXA-VARA OU ARTRITE IDIOPÁTICA JUVENIL?

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Key words: Idiopathic juvenile arthritis, childhood arthritis, camptodactily coxa-vara syndrome
Descritores: Artrite idiopática juvenil, artrite da criança, camptodactilia coxa-vara syndrome

Abstract

We describe the case of a 37 year old female patient with diagnosis of JIA (juvenile idiopathic arthritis) that was treated as such and whose radiological findings were consistent with the diagnosis of camptodactyly coxa-vara syndrome. **Endocrinol diabetes clin exp 2015 1818 -1819.**

Resumo

Descreve-se o caso de uma paciente de 37 anos, com diagnostico de AIJ (artrite idiopática juvenil) tendo sido tratada como tal, cujos achados radiológicos foram compatíveis com o diagnóstico de síndrome da camptodactilia coxa-vara. **Endocrinol diabetes clin exp 2015 1818 -1819.**

INTRODUCTION

The syndrome of arthropathy with camptodactyly, coxa vara and pericarditis (CACP) is a congenital disorder that manifests in children and that origins, as the name suggests, camptodactyly (flexion deformity of one or more proximal interphalangeal joints), arthropathy with a non-inflammatory synovial hyperplasia, progressive varus deformity of the hip and pericardial effusion (1). It is caused by homozygous defects of chromosome 1 1q25-31 region known as the CACP locus. This defect leads to changes of the PRG4 gene (Online Mendelian Inheritance in Man or OMIM number 208 250), that is implicated in the proteoglycans synthesis causing failure in the production of synovial fluid lubricin (1,2,3).

As it affects children and may present with pericardial effusion and multiple joints synovial effusion can often be confused with juvenile idiopathic arthritis (JIA) (1). However, this differential diagnosis is essential since the treatment of the two situations is quite different.

We describe here, a case of a 37 year old patient with CACP who had been diagnosed with juvenile idiopathic arthritis for many years, showing the differentiation difficulty between these two entities.

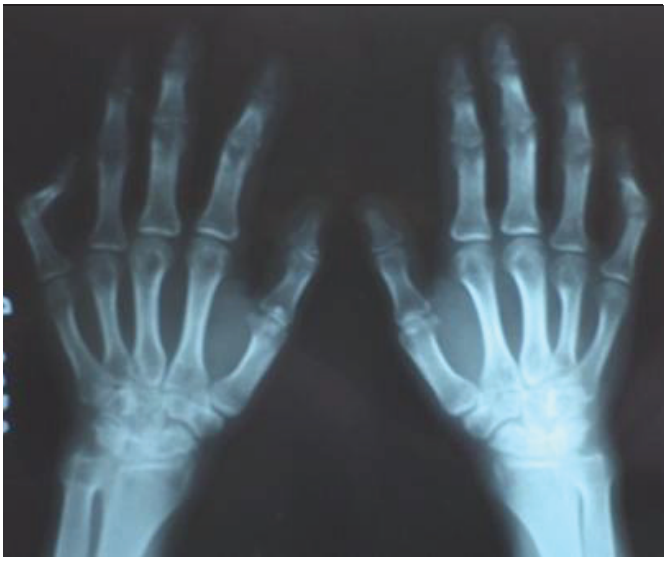
CASE REPORT

The patient was a 37 years old female, African descent, that was referred for treatment of arthritis (sic). Her disease began when she was 4 years old with knuckles, elbows, knees and ankles edema. She was treated as juvenile idiopathic arthritis and received weekly methotrexate. The treatment was stopped 10 years ago. There was a period without monitoring and she seeks medical attention now because of bilateral pain in both knees without edema.

The patient was diagnosed with depression and was using fluoxetine for at least, 5 years. She had smoked 12 cigarettes per day since adolescence. She also reported having two sisters, with similar symptoms and who were also diagnosed with juvenile arthritis. Maternal grandparents were first degree cousins.

Physical examination: Blood pressure 120x80 mm Hg, pulse 80. Temperature 37oC. Head and neck: sp. Heart, lungs and abdomen: sp. Rheumatologic examination showed: fifth fingers with fixed flexion at the level of the proximal interphalangeal, bilaterally; permanent defect of both elbows in flexion: 30o at right and 20o at left; mobilization pain at external rotation of the left hip and slight atrophy of the left quadriceps. There were crepitations in both knees. No signs of active arthritis were seen.

Laboratory examination showed a negative rheumatoid factor, red cell count with globular volume of 38%; 7,300 leukocytes / mm3. Anti HCV was negative and liver function tests were normal. ESR (sedimentation rate) was of 17mm. The radiologic pictures are in the figure 1 where it can be seen bilateral camptodactyly and enlargement of the femural neck, as well as osteoarthritis of the knees and hip joints.



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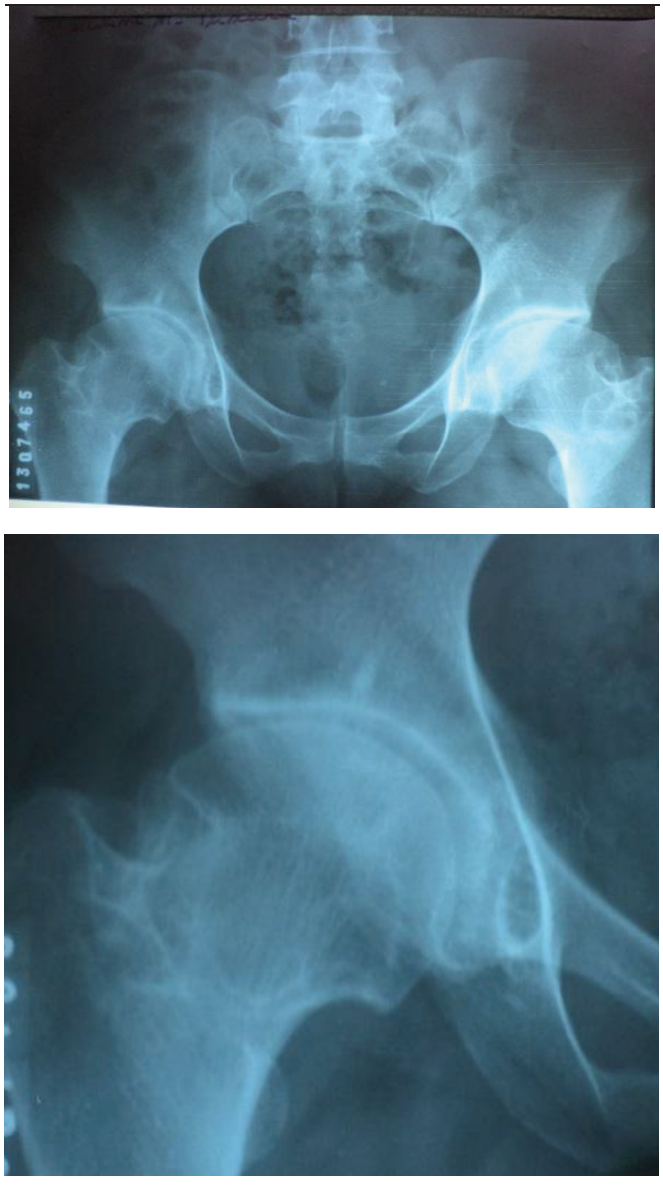

Figure 1- Radiological Images Showing Camptodactyly, Femur Neck Enlargement and Osteoarthritis in Hip and Knees.

She was diagnosed with camptodactyly-coxo vara syndrome by imaging studies and treated with analgesia and physiotherapy.

DISCUSSION

The arthropathy seen in CACP involves mainly the large joints such as elbows, hips, knees and ankles (1). The synovial fluid analysis shows a non-inflammatory synovial fluid. Histopathological examination revealed marked tissue hyperplasia of the synovium, with no inflammatory cell infiltration or vasculitis but with the presence of multinucleated giant cells (4). Radiological findings show deformities such as those seen in our patient and may have justarticular osteoporosis, without erosions. Intraosseous cysts filled with synovial fluid may be found (5).

In this disease, the camptodactyly is usually bilateral and may be congenital or appear in early childhood. The degree of contraction need not be the same for both hands and the deformity can progress with time (6). It must be distinguished from finger buttonhole classically found in rheumatoid diseases. Pericarditis is the presentation least commonly seen and, as can be mild and self-limited and it often goes overlooked. It occurs in approximately 30% of cases. Coxa vara appears in up to 90% of cases (6).

The studies of synovial fluid from a patient with CACP had shown that hyaluronic acid molecules assume a more rigid conformation due to lack of lubricin. Thus, the impact energy that occurs during the movement dissipates a very inefficient manner. According to Jay et al., 2007, lubricin acts as a chondroprotector (7). Laboratory tests, including analysis of inflammatory activity and presence of autoantibodies is negative (6).

In the reported patient it was observed some consanguinity between the maternal grandparents, which may have favored the development of the syndrome.

This condition must be distinguished from idiopathic juvenile arthritis whose treatment involves anti-inflammatory drugs, methotrexate and anti TNF alpha drugs, due to the inflammatory nature of the latter (7). The treatment of CACP is supportive with emphasis on physical therapy and the correction of deformities of the hands and thigh (6).

CONCLUSION

The authors conclude that the CACP syndrome should be considered in young patients with non-inflammatory arthropathy. Differentiation of JIA is clinically important in view of the large difference of the therapeutic approach in these two conditions and, in particular, because of the possible side effects associated with drugs used to treat JIA.

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ORIGINAL ARTICLE
PREVALENCE OF METABOLIC SYNDROME IN SYSTEMIC LUPUS ERYTHEMATOUS

PREVALÊNCIA DE SÍNDROME METABÓLICA EM LUPUS ERITEMATOSO SISTÊMICO

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*THELMA L SKARE

Key words: Systemic lupus erythematosus; Prognosis, Metabolic syndrome, Survival.
Descritores: Lúpus eritematosos sistêmico; Prognóstico; Síndrome metabólica; Sobrevida.

Abstract

Background: With advent of modern drugs, survival of Systemic Lupus Erythematous (SLE) patients has increased. Currently the biggest causes of death in this disease are infections and atherosclerosis. Therefore it is important to act preventively in these two complications. **Objective:** To describe the prevalence of metabolic syndrome (MS) in patients with SLE seen in the rheumatology unit of the Evangelic Hospital in Curitiba (HUEC). **Methods:** This is an observational cross-sectional study that included 119 patients treated at the HUEC Rheumatology Service diagnosed with SLE. We proceeded to the review of medical records for clinical, serological and treatment data. The activity of the disease was examined by SLEDAI (Systemic lupus disease activity index) and the presence of MS was diagnosed by the presence of the NCEP-ATPIII criteria (National Cholesterol Education Program - Adult Treatment Panel III). **Results:** MS was observed in 16% of patients. Patients with MS were older (p=0.02). We found a tendency to association of MS with the occurrence of serositis (p=0:08) and a positive association with glucocorticoids use (p=0.04); There was no association between MS and disease activity measured by SLEDAI (p=0.7). **Conclusion:** The prevalence of MS in this sample was of 16%. The degree of disease activity measured by the SLEDAI does not influence on its presence but a positive association was found with use of glucocorticoids. **Endocrinol diabetes clin exp 2015 1820 -1823.**

Resumo

Justificativa: Com advento de modernas armas terapêuticas, a sobrevivência dos pacientes de Lúpus Eritematoso Sistêmico (LES) tem aumentado. Atualmente as maiores causas de óbito nessa doença são as infecções e aterosclerose. Torna-se, portanto, importante atuar de maneira preventiva nestas duas complicações. **Objetivo:** Descrever a prevalência de síndrome metabólica em pacientes com lúpus eritematoso sistêmico, atendidos no ambulatório do Hospital Universitário Evangélico de Curitiba (HUEC). **Metodologia:** Estudo transversal observacional que incluiu 119 pacientes atendidos no Serviço de Reumatologia do HUEC, com diagnóstico de LES. Procedeu-se a revisão de prontuários para dados clínicos, sorológicos e de tratamento. Examinou-se a atividade da doença através do SLEDAI (*Systemic lúpus disease activity index*) e a presença de síndrome metabólica diagnosticada pela presença dos critérios de NCEP-ATPIII (National Cholesterol Education Program - Adult Treatment Panel III). **Resultados:** A síndrome metabólica foi observada em 16% dos pacientes. Pacientes com SM eram mais idosos (p = 0,02). Observou-se uma tendência para associação de síndrome metabólica com ocorrência de serosites (p=0.08) e associação positiva com uso de glicocorticoides (p= 0.04). Não se encontrou associação entre SM e atividade da doença medida pelo SLEDAI (p=0.7). Conclusão: A prevalência da síndrome metabólica nesse estudou foi de 16% nos pacientes com LES. O grau de atividade da doença medido pelo SLEDAI não influi no aparecimento da síndrome metabólica. O uso de glicocorticóide esteve associado ao seu aparecimento. **Endocrinol diabetes clin exp 2015 1820 -1823.**

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory connective tissue disease that is characterized by a pleomorphic involvement of several organs and systems (1). Its cause is unknown, but it seems to have influence of genetic and environmental factors (2). Although it can occur in both genders and at any age, it has a higher incidence in women, with peak incidence around 30 years (1). Diagnosis is made by the American College of Rheumatology classification criteria proposed in 1982 (3) and revised in 1997 (4).

With precocious diagnosis, improvement in the treatment of disease and in life support measures, there is a progressive increase in survival of SLE patients. In 1976 Urowitz et al. (5) observed a bimodal pattern of causes of death: the first peak related to disease activity and infections and the second to coronary artery disease (CAD). In subsequent years, others confirm this pattern and this curve became known as the Urowitz bimodal mortality curve.

Autoimmunity and the inflammatory process are directly related to changes in the lipid profile and lipoprotein metabolism in SLE (6). The dyslipoproteinemia standard of this disease is characterized by high levels of triglycerides (TG), and lipoprotein very low density (VLDL) associated to low levels of high density lipoprotein (HDL) (6). In addition to this, several drugs used in the treatment of SLE promote deleterious changes in the lipid profile, with particular importance for the effect of corticosteroids (7,8).

Metabolic syndrome (MS) is a risk factor for cardiovascular disease. It includes insulin resistance, dyslipidemia and central body fat deposition (9). SM contributes, in turn, to increase of overall mortality and 1.5 times to 2.5 times in cardiovascular disease. (10,11) According to the NCEP-ATPIII criteria (National Cholesterol Education Program - Adult Treatment Panel III) (9) SM occurs when three of the five following criteria are present: (a) - central obesity - waist circumference greater than 88 cm in women and 102 cm in man; (B) blood hypertension with systolic blood pressure> 130 mm Hg and/or diastolic blood pressure> 85 mmHg; (C) altered levels of fasting glucose (above 100 mg/dl) or known diabetes; (D) triglicerídes ≥ 150 mg/dl; HDL cholesterol<40 mg/dl in men and <50 mg/dl in women.

SLE patients appear to have a higher prevalence of MS

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than the general population (7,12) and this aggravates further the atherosclerotic risk in a population already susceptible to heart attacks and strokes.

This study was done to determine the prevalence of MS in Brazilian patients with SLE and its possible associations with disease and treatment profile.

MATERIAL AND METHODS

This study was approved by the Local Ethics Committee in Research and all participants signed informed consent. One hundred and nineteen patients with SLE according to the 1997 Classification criteria of American College of Rheumatology (4) and from a single rheumatologic center were studied. The data collection period was from August 2014 until April 2015.

Patients included had measurement of weight, height, waist and hip circumference and of arterial blood pressure. It was done a questionnaire for history of hypertension, diabetes mellitus and cardiovascular events (myocardial infarction, angina and stroke).The charts were reviewed for clinical data, presence of auto antibodies, drugs in current use. Disease activity was measured by the SLEDAI (13). Lipid profile and fasting blood glucose were measured.

Patients were classified as having or not MS according to the NCEP-ATPIII criteria (9) and the two groups were compared.

Patients with any other chronic inflammatory disease associated, untreated hypothyroidism and pregnant women] were excluded

The obtained data was grouped in frequency and contingency tables and the Kolmogorov-Smirnov test was used for the analysis of data distribution. Central tendency was expressed as mean and standard deviation (SD) for samples with Gaussian distribution of in median and inter quartile ranges (IQR) when the samples was not Gaussian. Fisher test and chi-square test were done to study association of nominal variables and Mann Whitney test and unpaired t test were used for numerical variables. Calculations were made with the assistance software Graph Pad Prism, version 4.0. Adopted significance was of 5%.

RESULTS

Of the 119 patients studied 14/119 (11.7%) were men and 105/119 (88.2%) women. Age ranged from 16 to 74 with average of 41.03 ± 12.19 years. Disease duration ranged from 1-28 years; median 7.0 IIQ of 4.0 to 28.0. As for the race: 94/119 (78.9%) were Caucasian and African descent were 25/119 (21.09%). The clinical data profile (defined according to the classification criteria of the ACR 1997) can be seen in Table 1.

TABLE 1. Clinical Data in 119 Systemic Lupus Erythematosus (SLE) Patients

Clinical data	N	%
Photosensitivity	18/119	15.1%
Malar Rash	63/119	52.9%
Aphtas	38/119	31.9%
Discoid lesions	39/119	32.7%
Arthritis	80/119	67.2%
Serositis (pleurisy, serositis, ascites)	21/119	17.6%
Glomerulonephritis	65/119	54.6%
Neurological involvement (psychosis and convulsions)	20/119	16.08%
Hematological involvement (hemolytic anemia, leukopenia, thrombocytopenia)	64/119	53.7%
Immune disorders (antiphospholipid, Sm or dsDNA)	41/119	34.4%
Antinuclear antibodies	118/119	99.1%

In Table 2 are the drugs currently in use in the study population.

TABLE 2 Medications Used to Treat SLE in 119 Patients

Drugs	N	%
Corticosteroids (Range from 5 to 40 mg; median of 5,00; IQR from 5.0-15.0	32/119	26.89%
Antimalarial drugs	107/119	89.9%
Azathioprine	24/119	20.1%
Cyclosporin	7/119	5.8%
Mycophenolate mofetil	12/119	10.08%
Cyclophosphamide	6/119	5.04%
Methotrexate	15/119	12.6%
Thalidomide	5/119	4.2%

Concerning the metabolic profile and the risk factors of the samples it was found: abdominal circumference from 52 to 145.0 cm (median 89.0; IIQ of 80.0 to 99.0); systolic blood pressure of 90 to 180 (median of 120.0, IIQ of 100-120); diastolic blood pressure 60-100 (median 80.0; IIQ of 60.0 to 80.0); 63,0-200.0 mg glucose/dl (mean 87.0; IQR of 81.0 to 94.75 mg/dL); triglycerides from 34.00 to 419.0 (median 92.6; IIQ of 74.0 to 128.8); HDL cholesterol 23.0 to 135.0 (median 47.0 IQR of 40.0 to 58.75); history of angina in 11/119 or 9.2%; history of stroke (AVE) in 5/119 or 4.2%; history of acute myocardial infarction in 6/119 or 5.04% and smoking in 19/119- 15.9%. In this population the SLEDAI ranged from 0-36 (median 16.0; IIQ of 12.0 to 26.0).

The prevalence of metabolic syndrome in SLE population described above was 20/119 - 16.08%.

In the data comparison between SLE patients with and without MS found the data of table 3.

TABLE 3 - Comparison of SLE Patients with and without Metabolic Syndrome (MS)

	With MS N=20	Without MS N=99	P
Gender	17 females/3 males	88 females/11 males	0,70*
Median disease duration in years	Median 6,5(2,6-14,7)	Median 7,0 (4,0-9,0)	0,93**
Mean age at disease onset (years)	37,50±15,1	32,56±10,4	0,14***
Tobacco exposure	5/20 -25%	14/99 -14,4%	0,31 *
Ethnic background (caucasian/afrodescendants)	17/3	78 /21	0,76*
Photossensitivity	13/20 –65%	65/99 – 65,6%	0,95****
Malar rash	10/20 – 50%	53/99- 53,5%	0,77****
Aphtas	7/20- 35%	31/99 – 31,3%	0,74****
Lesão discóide	4/20 -20%	35/99- 35,3%	0,20*
Artrithis	15/20 - 75%	65/99 – 65,5%	0,41****
Serositis (pleuritis, pericarditis, ascitis)	6/20 – 30-%	15/99 – 15,1%	0,08****
Glomerulonephritis	11/20 -55%	54/99 - 54,4%	0,79****
Neurological involvement (psychosis and convulsions)	3/20 – 15%	17/99 -17,1%	1,00 *
Hematological involvement (hemolytic anemia, leukopenia, thrombocytopenia)	13/20 – 65%	51/99- 51,5%	0,26****
Immune disorders (antiphospholipid, Sm or dsDNA)	9/20- 45%	32/99 – 32,3%	0,27****
Antinuclear antibodies	20/20 – 100%	98/99- 98,9%	1,0*
Antimalarial use	16/20 - 80%	91/99- 91,9%	0,11*
Azathioprine use	6/20 – 30%	18/99 – 18,1%	0,22****
Cyclosporine use	0/20	4/99 - 4,0%	1,00*
mycophenolate mofetil use	4/20 - 20%	8/99 - 8,08%	0,10*
cyclophosphamide use	2/20 – 10%	4/99- 4,04%	0,26*
Metothrexate use	3/20 – 15%	12/99 – 12,1%	0,71*
Thalidomide use	0	5/99 – 5,05%	0,58*
Acute myocardial infarction history	4/20 – 20%	2/99 – 2,02%	0,006*
Angina history	4/20 – 20%	7/99 - 7,07%	0,07*
Stroke history	0/20 -0	5/99 – 5,05	1,00*
Median SLEDAI	19,0 (12,5-26,7)	16,0 (12,0-26,0)	0,72**

**Fisher* ***Mann Whitney* ****Teste t não pareado* *****Qui quadrado*

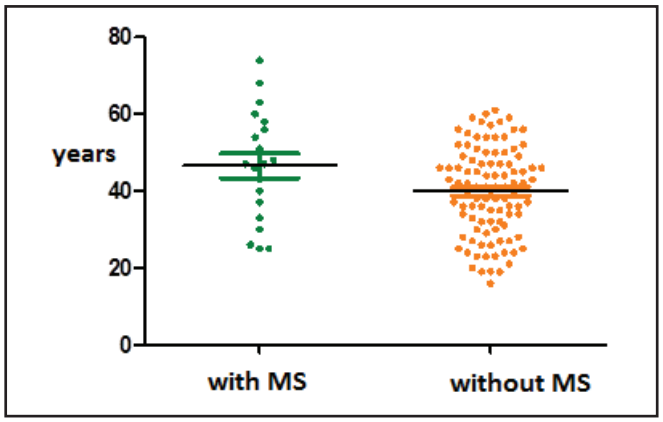

FIGURE 1. Comparison of SLE Patients with and without Metabolic Syndrome in the Category Present Age.
Patients with MS were aged 25-74 years (mean 46.5 ± 14.3) and without MS aged 16.0 to 61.0 (average 39.92 years) with p = 0.0259 (Trial unpaired t).

The SM analysis regarding use of corticosteroids may be appreciated in Figure 2 .

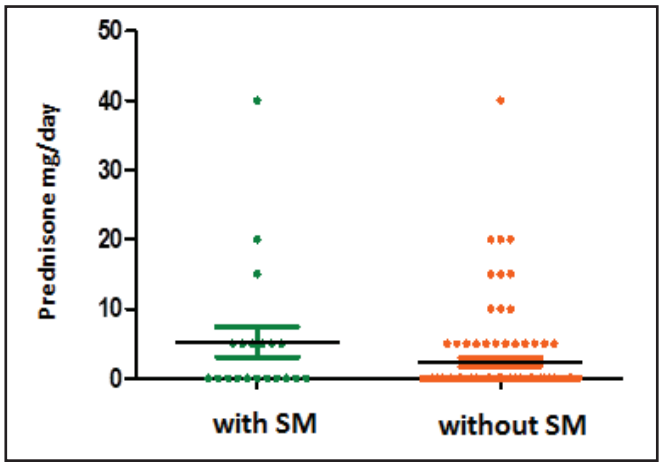

FIGURE 2 - Comparison of SLE Patients in the Question Use of Corticosteroids with or without Metabolic Syndrome .
About 9/20 or 45% of patients with MS were using this medicine against 23/99 or 23.3% of the patients without MS; p = 0.0452 (chi-square test). As regards the daily dose of prednisone, median patients who had SM was Median 0; IIQ of 0-5.0 and without the SM was 0; IQI of 0.0 to 0.0 p = 0.0426 (Mann Whitney test)

DISCUSSION

According to the results obtained in this study 16% of SLE patients with have metabolic syndrome even though the studied sample was relatively young (mean age 41 years). The prevalence of metabolic syndrome in this study the same (16%) of a research of 141 SLE patients done by Bultinki et al. (14) which found association with intravenous methylprednisolone use, renal insufficiency, older age, higher ESR (erythrocyte sedimentation rate) and higher C3 levels. However our result was lower than those found by Telles et al (15) that studied 162 SLE Brazilian patients and found a prevalence of 32.1%.

It was also observed that patients using corticosteroids and that have advanced age are more prone to the development of MS. Furthermore, there was a greater tendency for MS in patients with clinical data as serositis.

As might be expected the frequency of acute myocardial infarction (AMI) and angina was higher in patients with SLE and with MS, when compared to the SLE group without MS (20% vs 2.02% in AMI, 20% vs. 7.07% in angina). This finding can be supported by the study by García-Villegas et al (17) that found that the cumulative incidence of CVD in a lupus group with MS was 17.3% and in the group without MS it was 7.0% with a relative risk of 2.48. This finding reinforces the need to employ all the efforts to fight SM beside with SLE treatment.

Our research has shown that 45% of patients with MS were using corticosteroids against 23.3% of patients without MS. The influence of glucocorticoid in SM has been noted by others (18) . The association of SM with corticosteroid therapy may be related to the fact that one of the criteria of SM is increased waist circumference. Some medications such as corticosteroids can cause weight gain and change the distribution of body fat (19) and central obesity carries greater risk of cardiovascular disease and premature death. In addition, glucocorticoids may also have a variety of actions that lead to hyperglycemia or an exacerbation of preexisting diabetes. The mechanism by which they cause hyperglycemia is multifactorial, including augmentation of hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue, and alteration of receptor and post-receptor functions (20). They also promote peripheral insulin resistance, hyperinsulinemia, and increased hepatic very low-density lipoprotein (VLDL) synthesis (20).

This association of SM with corticosteroids is of fundamental importance and brings to light the need of rheumatologist awareness for use of disease-modifying drugs earlier and more effectively limiting the use of glucocorticoids to the lowest dose and for the shortest time possible.

CONCLUSION

The prevalence of metabolic syndrome in this studied was 16% in SLE patients, and these patients are more likely to have as clinical manifestation to serositis. The degree of disease activity measured by the SLEDAI does not influence the onset of metabolic syndrome. Glucocorticoid users and older individuals were more SM.

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