UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

TESE DE DOUTORADO

Síndrome Metabólica, Cálcio Coronário e Homeostase Pressórica em Pacientes com Diabetes Melito Tipo 1

TICIANA DA COSTA RODRIGUES

Porto Alegre, abril de 2008

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Orientador: Prof. Dr. Jorge Luiz Gross

Porto Alegre, abril de 2008

DEDICATÓRIA

Aos meus pais.

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SUMÁRIO

Agradecimentos..... iv

Lista de Tabelas e Figuras..... ix

Lista de Abreviaturas..... x

CAPÍTULO 1

O Papel da Síndrome Metabólica e da Resistência à Ação da Insulina na Doença Cardiovascular em Pacientes com Diabetes Melito Tipo 1

Resumo..... 13

Abstract..... 13

1. Introdução..... 14

2. Critérios Diagnósticos da Síndrome Metabólica..... 15

3. Métodos de Avaliação de Resistência Insulínica..... 15

4.A Doença Cardiovascular no Paciente com Diabetes Melito Tipo 1..... 17

5. O Impacto da Resistência Insulínica e Síndrome Metabólica no Diabetes Melito tipo 1 20

6. Conclusões 24

7. Referências ……..... 25

CAPÍTULO 2

Metabolic Syndrome, Hypertension and Microvascular Complications and Coronary Calcium Score in Type 1 Diabetes

Abstract…….. 38

Introduction…….……... 40

Research design and methods…… 41

Results……..... 43

Conclusions……..... 45

References……..... 48

CAPÍTULO 3

Coronary Artery Calcification in Women with Type 1 Diabetes is Associated with Insulin Resistance Index

Abstract……..……. 57

Manuscript ……...…….....…..... 58

References……..... 63

CAPÍTULO 4

Masked Hypertension, Night-time Blood Pressure and Diabetic Retinopathy in Patients with type 1 Diabetes

Abstract…….....…….. 70

Introduction…….....…… 71

Research design and methods…….....… 71

Results……..... 74

Conclusions…….....……... 75

References…….....……. 81

LISTA DE TABELAS E FIGURAS

CAPÍTULO 1

Tabela 1. Critérios diagnósticos da SM segundo as 3 definições mais utilizadas: OMS, NCEP-ATP III e IDF..... 35

CAPÍTULO 2

Table 1. Descriptive data for patients with and without metabolic syndrome..... 52

Figure 1 Coronary artery calcification in women and men marked according to the presence or absence of metabolic syndrome 54

CAPÍTULO 3

Table 1. Clinical characteristics of patients with and without coronary artery calcification …… . 66

Table 2 Laboratory data of patients with and without coronary artery calcification ….....…… 67

CAPÍTULO 4

Table 1. Clinical and laboratory data according to the blood pressure profile…..… 78

Table 2. Blood pressure parameters in patients with type 1 diabetes with normotension and masked hypertension…….. 79

Table 3. Blood pressure parameters in patients with type 1 diabetes without retinopathy and with retinopathy…… 80

LISTA DE ABREVIATURAS

ABPM	*Ambulatory blood pressure monitoring*
BMI	*Body mass index*
BP	*Blood pressure*
CAC	Calcificações em artérias coronárias
CAC	*Coronary artery calcium*
CI	*Confidence interval*
DCV	Doença Cardiovascular
DM	Diabetes melito
DN	*Diabetic Nephropathy*
DR	*Diabetic Retinopathy*
ESRD	*End-stage renal disease*
EUA	Excreção urinária de albumina
GDR	*Glucose disposal rate*
GFR	*Glomerular filtration rate*
HAS	Hipertensão arterial sistêmica
IDF	*International Diabetes Federation*
MetS	*Metabolic Syndrome*
NCEP-ATP	*National Cholesterol Education Program´s Adults Treatment Panel*
ND	Nefropatia diabética
PA	Pressão arterial
OMS	Organização Mundial da Saúde
OR	*odds ratio*

RD	Retinopatia diabética
RI	Resistência à ação da insulina
SM	Síndrome metabólica
SD	*Standard deviation*
TFG	Taxa de filtração glomerular
UAER	*Urinary albumin excretion rate*
WHR	*Waist/hip ratio*

CAPÍTULO 1

O Papel da Síndrome Metabólica e da Resistência à Ação da Insulina na Doença Cardiovascular em Pacientes com Diabetes Melito Tipo 1

"The Role of Metabolic Syndrome and Insulin Resistance in the Cardiovascular Disease of Patients with Type 1 Diabetes"

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Resumo

A síndrome metabólica (SM) é um transtorno complexo representado por um conjunto de fatores de risco cardiovasculares relacionados à deposição central de gordura e à resistência à ação da insulina (RI), e está associada à mortalidade precoce em indivíduos não-diabéticos e em pacientes com diabetes melito (DM) tipo 2.

A presença da SM e dos seus componentes tem sido descrita também em pacientes com DM tipo 1 e pode contribuir para o elevado risco de doença cardiovascular observado nesta população de pacientes.

O objetivo deste trabalho foi revisar as evidências disponíveis sobre o papel da SM e da RI no desenvolvimento da doença cardiovascular nos pacientes com DM tipo 1.

Descritores: síndrome metabólica, resistência à ação da insulina, doença cardiovascular, diabetes melito tipo 1

Abstract

Metabolic syndrome (MetS) is a complex disorder represented by a set of cardiovascular risk factors related to the central adiposity and insulin resistance (IR) and it is associated with early mortality in non-diabetic subjects and in patients with type 2 diabetes.

The presence of MetS and its components have also been reported in patients with type 1 diabetes and may contribute to the high risk of cardiovascular disease observed in this population of patients.

The aim of this study was to review the available evidence about the role of MetS and IR in the development of cardiovascular disease in patients with type 1 diabetes .

Key words: Metabolic syndrome, insulin resistance, cardiovascular disease, type 1 diabetes

Introdução

A síndrome metabólica (SM) é um transtorno complexo representado por um conjunto de fatores de risco cardiovasculares relacionados à deposição central de gordura e à resistência à ação da insulina (RI)[1]. Entre estes fatores de risco, incluem-se a dislipidemia, a obesidade centrípeta, a alteração na homeostase glicêmica e a hipertensão arterial sistêmica. A prevalência de SM na população em geral é de aproximadamente 24%[2] chegando a mais de 80% entre os pacientes com diabetes melito (DM) tipo 2[3]. A SM é um importante fator de risco de mortalidade precoce em indivíduos não-diabéticos [4,5] e em pacientes com DM tipo 2[4]. Entretanto, o papel da SM como entidade independente e associada a um maior risco para o desenvolvimento de eventos cardiovasculares tem sido recentemente questionado[6].-

A presença da SM e dos seus componentes tem sido descrita também em pacientes com DM tipo 1, e pode estar associada à presença de nefropatia diabética (ND) e à piora do controle glicêmico[7].

Embora o risco absoluto de doença cardiovascular (DCV) em pacientes com DM tipo 1 seja menor do que nos pacientes com DM tipo 2, ele está drasticamente elevado quando comparado aos indivíduos não-diabéticos de mesma idade[8]. Os fatores de risco clássicos e a presença de ND explicam apenas parcialmente esta observação[9]. A hipótese de que a presença da SM em pacientes com DM tipo 1 poderia se constituir em um fator de risco para DCV apresenta uma fundamentação teórica. A presença de RI tem sido descrita em pacientes com DM tipo 1[9-11] e pode contribuir para o elevado risco de DCV observado nesta população de pacientes. Os estudos que analisaram o papel da SM como fator de risco para as complicações micro-e macrovasculares são escassos e foram conduzidos em populações selecionadas.

O objetivo deste trabalho foi revisar as evidências disponíveis do papel da SM e da RI no desenvolvimento da DCV em pacientes com DM tipo 1.

Critérios Diagnósticos da Síndrome Metabólica

Existem várias propostas de definição clínica de SM. Três são as mais utilizadas: Organização Mundial da Saúde (OMS)[12], *National Cholesterol Education Program´s Adults Treatment Panel III* (NCEP-ATP III)[13], e, mais recentemente, a *International Diabetes Federation* (IDF)[14]. A definição da OMS foi proposta em 1998 e preconiza como ponto de partida a avaliação da RI ou do distúrbio do metabolismo da glicose e inclui a medida da albuminúria e por isso é mais complexa de ser avaliada. A definição do NCEP-ATP III foi desenvolvida para uso clínico e não exige a comprovação de RI. Pela sua simplicidade e praticidade esta é a definição recomendada pela I Diretriz Brasileira de Diagnóstico e Tratamento da Síndrome Metabólica[15]. Durante a convenção sobre SM e pré-diabetes realizada em Berlim no ano de 2005, foi apresentada outra definição que coloca a adiposidade central como componente principal. Além disto, os pontos de coorte de circunferência da cintura são mais baixos do que na definição do NCEP e há valores específicos para os diferentes grupos étnicos[14,16]. Os critérios das três propostas estão descritos na tabela 1.

Métodos de Avaliação de Resistência à Ação da Insulina

Acredita-se que a RI seja o principal fator patogênico da SM[17]. Tradicionalmente o conceito de RI é definido como um defeito na ação da insulina que resulta em uma hiperinsulinemia compensatória para manter os níveis de glicemia dentro da normalidade. Um importante fator de contribuição para a RI é a presença de níveis séricos elevados de ácidos graxos livres, provenientes do aumento da mobilização de triglicerídeos do tecido adiposo[17].

O padrão ouro para a avaliação de RI é o estudo de *clamp* hiperinsulinêmico euglicêmico[18]. De forma simplificada, este é realizado através de um acesso venoso e administração de insulina com o objetivo de suprimir a produção endógena de glicose e aumentar a sua captação fisiológica. Para manter os níveis glicêmicos entre 90 e 140 mg/dl, há a infusão de glicose intravenosa. A sensibilidade à ação da insulina é quantificada pela taxa de infusão de glicose necessária para manter os níveis glicêmicos dentro das metas estabelecidas[18]. Em função da dificuldade de execução dos estudos de clampeamento, outras formas de avaliação da RI foram desenvolvidas. Por mais de duas décadas, a insulina de jejum foi utilizada como marcador de sensibilidade insulínica em vários estudos epidemiológicos, assumindo que a insulina de jejum seria um equivalente de RI[18,19]. Porém, a insulina de jejum não pode explicar mais de 30 a 40% da variação de sensibilidade insulínica encontrada no clampeamento[20]. Um método melhor, mas ainda não ideal, de estimar a RI é *Homeostasis Model Assessment* (HOMA-IR) desenvolvido por Matthews e colaboradores, utilizando um modelo matemático que leva em consideração os níveis de glicemia e de insulina séricos[21]. O HOMA-IR possui uma correlação estreita com os resultados do clampeamento em relação a RI [21,22]. Porém, em pacientes usuários de insulina, como nos pacientes com DM tipo 1, tanto a dosagem de insulina sérica, quanto a utilização do HOMA são inválidos, fazendo-se necessária uma outra forma de avaliação de RI.

Marcadores clínicos podem identificar pacientes com RI[23]. Além das tradicionais características clínicas de hipertensão arterial, razão cintura/quadril, história familiar de DM tipo 2, níveis de triglicerídeos e HDL colesterol, também o mau controle glicêmico e a dose total de insulina são associados à RI[24]. A partir destas informações foi desenvolvido e validado um escore de avaliação de RI, denominado de *glucose disposal rate* (GDR),

utilizando a técnica de *clamp* hiperinsulinêmico euglicêmico (60 mU. $m^{-2}.min^{-1}$)[24] em um grupo de pacientes com DM tipo 1. Esta avaliação deu origem à seguinte equação :

GDR ($mg.kg^{-1}.min^{-1}$) = 24,31 – 12,22 x (razão cintura/quadril) – 3,29 x (presença de hipertensão arterial) – 0,57 x (HbA1).

Presença de hipertensão arterial = 1 e ausência = 0. Esta equação foi modificada para a utilização de Hb_{A1c} no lugar de HbA1 (7), tendo atualmente a seguinte descrição:

GDR ($mg.kg^{-1}.min^{-1}$) = 24,4 – 12,97 x (razão cintura/quadril) – 3,39 x (presença de hipertensão arterial) – 0,60 x (Hb_{A1c}).

Diversos estudos têm utilizado esta equação como método de avaliação de RI em pacientes com DM tipo 1 [7, 9, 25, 26].

A Doença Cardiovascular no Paciente com Diabetes Melito Tipo 1

A DCV aterosclerótica, especialmente a doença arterial coronariana (DAC) é a principal causa de mortalidade e morbidade no paciente com DM [27]. A maior ocorrência de mortalidade por DAC em pacientes com DM tipo 1 já tem sido relatada desde a década de setenta[28]. Krolewski e colaboradores demonstraram que aos 55 anos de idade a taxa de mortalidade cumulativa nesta população era de 30-40%, comparada à mortalidade de 4-8% em pacientes não-diabéticos descrita no estudo *Framingham*[29]. Dados do *Wisconsin Epidemiologic Study of Diabetic Retinopathy* (WESDR) relatam um risco de mortalidade por DAC de 9,1 para homens e de 13,5 para mulheres, em pacientes com diagnóstico de diabetes antes dos 30 anos de idade em relação à população em geral no período de 8 anos de seguimento[30]. Recentemente, um estudo prospectivo que acompanhou uma coorte de mais de sete mil pacientes com DM tipo 1 com 7 anos de seguimento, demonstrou que o risco relativo de eventos cardiovasculares foi de 3,6 (95% IC 2,9-4,5) para homens e de 7,7 (95% IC 5,5-10,7) para mulheres quando comparados com indivíduos não-diabéticos[31]. Este

mesmo estudo estimou em 5% o risco de DCV fatal nos próximos 10 anos para um indivíduo diabético com 50 anos de idade, o que corresponde a 10 a 15 anos antes do mesmo risco estar presente na população não-diabética. O seguimento de 23.751 pacientes com DM diagnosticado antes dos 30 anos de idade e tratados com insulina observou taxas de mortalidade semelhantes às descritas previamente e evidenciou que outras formas de DCV como hipertensão arterial, doença valvular, cardiomiopatia, insuficiência cardíaca e acidente vascular cerebral também estão elevadas nesta população de pacientes[32]. Estudos anátomo-patológicos e de ultrassonografia endovascular demonstraram ateromatose e anormalidades na parede coronariana consistentes com DAC precoce em pacientes com DM tipo 1[33, 34].

Embora a associação de DCV precoce em pacientes com DM tipo 1 seja conhecida há bastante tempo, a patogênese envolvida ainda não é completamente entendida. A hiperglicemia é, *a priori*, o mais importante fator responsável pela elevada incidência de DCV[35]. Entretanto, apesar de recente evidência de que o melhor controle glicêmico tenha sido associado à redução de DCV[36], a literatura é conflitante na associação de DCV e glicemia em pacientes com DM tipo 1. Enquanto alguns estudos afirmam que o controle glicêmico, após ajuste para os tradicionais fatores de risco de DCV, não esta significativamente associado com eventos cardiovasculares[9,37-39], outros estudos apontam para uma associação positiva[36, 40-42]. Uma meta-análise recente de ensaios clínicos mostrou que o melhor controle glicêmico reduziu a incidência de DCV em pacientes com diabetes tipo 1 e 2[41]. O efeito benéfico do controle glicêmico intensivo por 6 anos nos desfechos cardiovasculares foi confirmado após 11 anos de seguimento em pacientes com DM tipo 1[42]. E mais recentemente, uma análise após 16 anos de seguimento mostrou que a variação positiva de hemoglobina glicada foi fortemente associada a DCV e coronariana, e que parte

das discrepâncias nos resultados dos estudos anteriores podem ser conseqüência das diferentes prevalências de doença renal[36].

As recomendações européias não consideram o paciente com DM tipo 1 como de alto risco, a menos que microalbuminúria esteja presente[43]. Estudo recente que avaliou um grupo de pacientes com DM tipo 1 com doença de longa duração e assintomáticos para queixas cardiovasculares observou associação de doença aterosclerótica em coronárias, mas não em aorta, com nefropatia diabética[44]. Pacientes com DM tipo 1 e perda de função renal geralmente desenvolvem doença aterosclerótica extensa[45].

O elevado risco de DCV observado em pacientes do sexo feminino com DM tipo 1 não é explicado pelos tradicionais fatores de risco de DCV[46], e ainda não são completamente conhecidos os mecanismos envolvidos.

Estudo prospectivo que avaliou os fatores de risco associados ao desenvolvimento de DCV observou que nefropatia (especialmente em homens), hipertensão, fumo, dislipidemia, sintomas depressivos e RI foram todos relacionados ao desfecho CV em pacientes com DM tipo 1[9]. O controle glicêmico não foi associado com eventos cardiovasculares, mas manteve sua estreita relação com doença microvascular.

A presença de calcificações em artérias coronárias (CAC) tem uma excelente correlação ($r > 0,9$) com aterosclerose coronariana, sendo útil como medida de extensão de aterosclerose[47]. A presença de CAC prediz eventos cardiovasculares especialmente em indivíduos assintomáticos[48]. Pacientes com DM tipo 1 possuem maior quantidade de CAC em comparação com indivíduos não-diabéticos[49,50], o que favorece a hipótese de aterosclerose acelerada nestes pacientes. A presença de CAC, neste grupo de pacientes foi associada à doença clínica e presença de fatores de risco de DCV[51]. A avaliação de estudos com a presença de CAC em pacientes com DM tipo 1 mostrou que a presença de qualquer

quantidade de cálcio aumenta o risco de DCV[35]. Estudos prévios têm confirmado o maior risco de DAC em mulheres com DM tipo 1[31,49]. A avaliação de um grupo de pacientes com DM tipo 1 mostrou que a presença de CAC nas mulheres pode se dever a maior RI observada neste grupo de pacientes, especialmente associada a distribuição de gordura corporal[49].

O Impacto da Síndrome Metabólica e da Resistência à Ação da Insulina no Diabetes Melito Tipo 1

O primeiro estudo que avaliou pacientes com DM tipo 1 e presença de SM observou uma prevalência de 38% em homens e de 40% em mulheres[7]. Nos pacientes sem doença renal, nos microalbuminúricos, nos macroalbuminúricos e nos pacientes com doença renal terminal a prevalência de SM observada foi de 28%, 44%, 62% e 68% respectivamente[7]. A freqüência de SM também foi maior quanto pior o controle glicêmico desses pacientes. Todos os componentes separadamente da síndrome foram associados à ND. Mais recentemente, a prevalência da SM em pacientes com DM tipo 1 tem sido mais diversa, variando desde 12,5 a 42%[26,31,52]. Estas variações podem ser explicadas por diferentes níveis de RI e de faixa etária entre as populações estudadas.

A SM e a RI são características do DM tipo 2. A presença de SM pelos critérios da OMS está associada à presença de complicações micro e macrovasculares em pacientes com DM tipo 2[3,53]. Em pacientes com DM tipo 1 esta associação precisa ser melhor entendida, mas em relação a RI parece ser semelhante, uma vez que a RI foi associada à presença de retinopatia diabética (RD)[54], ND[53,55-57] e DCV[25] .

Pacientes com DM tipo 1 e microalbuminúria com discreta redução da taxa de filtração glomerular (TFG) possuem maior grau de RI, quando comparados a pacientes com

microalbuminúria sem redução da TFG e pacientes sem nefropatia[56]. Entretanto, pacientes com nefropatia possuem níveis elevados de pressão arterial, dislipidemia, baixo grau de inflamação e RI secundária à insuficiência renal, tornando difícil à distinção entre nefropatia e SM[56,58]. A RI avaliada através da utilização do *clamp* hiperinsulinêmico euglicêmico, é capaz de predizer o desenvolvimento de microalbuminúria[57].

Dados de estudos prospectivos nos auxiliam no entendimento destas relações. Uma análise que avaliou pacientes com diabetes tipo 1 e tipo 2, demonstrou que nos primeiros a presença de SM foi associada ao desenvolvimento de nefropatia e de neuropatia[53]. Uma avaliação realizada após 9 anos de seguimento, demonstrou que a RI estimada pela equação GDR foi capaz de identificar pacientes que desenvolveram nefropatia, retinopatia e DCV[59]. A presença de SM ou a dose de insulina inicialmente administrada não tiveram este poder. Os pacientes que participaram do grupo de tratamento intensivo e que apresentaram maior ganho de peso tiveram maior incidência de SM[59]. Outra avaliação prospectiva de 11 anos de seguimento em um pequeno grupo de pacientes com DM tipo 1 também não mostrou associação entre a presença de SM e o desenvolvimento de DCV, a SM não adicionou valor prognóstico aos já tradicionais fatores de risco de DCV[52]. Apenas um único estudo observou que a presença de SM, pelos 3 critérios conhecidos (OMS, NCEP e IDF) foi capaz de predizer risco de DAC e doença renal em pacientes com DM tipo 1, mas seus componentes individuais tiveram maior poder, especialmente a presença de microalbuminúria no critério da OMS[26].

Apesar de que a deficiência insulínica seja o defeito metabólico primário nos pacientes com DM tipo 1, os estudos descritos acima demonstram que a RI é um achado freqüente e que, em parte, pode contribuir para as elevadas taxas de eventos vasculares nessa população.

A administração exógena de insulina suficiente para atingir níveis adequados na circulação portal e manter a euglicemia produz hiperinsulinemia sistêmica. Tem sido proposto que essa hiperinsulinemia seria responsável pelo acúmulo de gordura abdominal nos pacientes com DM tipo 1[60]. O mecanismo proposto é de que a insulina aumenta a atividade da 11β-hidroxiesteróide-desidrogenase, especialmente nos adipócitos do omento, favorecendo o hipercortisolismo e aumentando a diferenciação das células estromais a adipócitos, promovendo obesidade abdominal [61-63].

Uma análise realizada quatro anos após o encerramento do *Diabetes Control and Complications Trial* (DCCT) demonstrou que os pacientes submetidos ao tratamento intensivo e que apresentaram maior ganho de peso apresentavam um índice cintura-quadril aumentado, maiores níveis de pressão arterial e maior necessidade de insulina para um melhor controle metabólico quando comparados aos pacientes que não obtiveram um ganho exagerado de peso. Estes pacientes também apresentaram um perfil lipídico mais aterogênico, assim como alteração de enzimas hepáticas, o que poderia ser explicado por uma conseqüência da SM em função do ganho de peso neste grupo de pacientes com DM tipo 1[59].

A avaliação de pacientes com DM tipo 1 classificados de acordo com seu peso corporal, demonstrou que pacientes com sobrepeso possuem maior prevalência de retinopatia e neuropatia diabéticas, porém após a análise de regressão, os maiores determinantes foram ainda controle glicêmico e duração do DM[54].

O uso de sensibilizador de insulina (rosiglitazona) em pacientes com DM tipo 1 com excesso de peso, resulta em melhora glicêmica e controle dos níveis de pressão arterial sem a necessidade de aumento da dose de insulina. Este resultado foi mais

pronunciado em pacientes com marcadores de RI, especialmente naqueles com IMC >30 kg/m^2 [64]. O uso de outro sensibilizador de insulina (metformina) em adultos e adolescentes com DM tipo 1 também melhora o controle glicêmico e reduz a necessidade de insulina nesses pacientes [65-68].

Em uma grande coorte de pacientes com DM tipo 1, os níveis de lipídeos foram associados ao hábito de fumar e à adiposidade abdominal, caracterizando a síndrome de RI[69].

Realizamos um estudo transversal em 100 pacientes com DM tipo 1 para a avaliação da associação de SM e presença de CAC. Observamos uma associação entre a presença de CAC e SM, especialmente em pacientes do sexo feminino. A hipertensão arterial foi o fator de risco individual da SM associado à presença de CAC. Esta observação reforça o papel da RI no paciente com DM tipo 1. A SM pode ter um impacto clínico e repercussão mais severa na aterosclerose das pacientes com DM tipo 1 do sexo feminino [70].

Conclusão

A DCV é a principal causa de mortalidade em pacientes com DM tipo 1, assim como nos pacientes com DM tipo 2.

Os marcadores de RI estão associados com complicações micro-e macrovasculares em pacientes com DM tipo 1. A RI é um dos pilares da SM. Em indivíduos com diabetes tipo 2 e em não-diabéticos a SM é um importante fator de risco cardiovascular. Nos pacientes com DM tipo 1, a associação de SM e RI com nefropatia é bastante evidente, mas a SM isoladamente não parece predizer DCV. A presença da SM pode ter um impacto mais acentuado na aterosclerose das pacientes do sexo feminino com DM tipo 1.

Os benefícios da melhora no cuidado com o DM ainda não parecem ter reduzido a mortalidade por DCV nos pacientes com DM tipo 1. Possivelmente devemos mudar nosso olhar sobre estes pacientes, além de perseguirmos as metas ideais de controle glicêmico, pressórico e lipídico, também devemos intensificar os esforços no controle de peso corporal, um fator de risco modificável e associado com a presença de RI.

Referências:

1- Kahn R, Buse J, Ferrannini E, Stern M. The Metabolic Syndrome: Time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2005; 28:2289-304.

2- Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: finding from the Third National Health and Nutrition Examination Survey. JAMA. 2002; 287: 356-9.

3- Costa LA, Canani LH, Lisbôa HR, Tres GS, Gross JL: Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in Type 2 diabetes**.** Diabet Med. 2004; 21:252-5.

4- Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissen M, Taskinen M-R, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001; 24: 683-9.

5- Lakka H-M, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA. 2002; 288: 2709-16.

6- Gale EA: Should we dump the metabolic syndrome? Yes. BMJ. 2008; 336: 640-641.

7- Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Wadén J, Rönnback M, Rosengård-Bärlund M, Björkesten CG, Taskinen MR, Groop PH: FinnDiane Study Group. Metabolic syndrome in type 1 diabetes. Association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005; 28: 2019-24.

8- Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ: American Heart Association; American Diabetes Association. Primary Prevention of Cardiovascular disease in people with diabetes mellitus. A scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2007; 30: 162- 72.

9- Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY-Z, Smithline Kinder L, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10 year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications study. Diabetes Care. 2003; 26:1374-79.

10- Stuhldreher WL, Orchard TJ, Ellis D. The association of waist-hip ratio and risk factors for development of IDDM complications in an IDDM adults population. Diabetes Res Clin Pract. 1992; 17: 99-109.

11- Stuhldreher WL, Becker DJ, Drash AL, Ellis D, Kuller LH, Wolfson SK, Orchard TJ. The association of waist-hip ratio with diabetes complications in an adult IDDM population. J Clin Epidemiol. 1994; 47: 447-56.

12- Alberti KG, Zimmet PZ for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. Diabet Med. 1998; 15: 539-53.

13- Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Cholesterol. JAMA. 2001; 285: 2486-97.

14- The IDF consensus world definition of the metabolic syndrome. Available from http://www.idf.org/webdata/docs/IDF_Metas_def_final.pdf . Acessado em 22 de março de 2008.

15- I Diretriz Brasileira de Diagnóstico e Tratamento da Síndrome Metabólica. Arq Bras Cardiol. 2005; 84:01-28.

16- Holt RI. International Diabetes Federation Re-defines the Metabolic Syndrome. Diabetes Obes Metab. 2005; 7: 618- 20.

17- Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005; 365:1415-28.

18- DeFronzo RA. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia, and atherosclerosis. Neth J Med. 1997; 50: 191-7.

19- Zavaroni I, Bonora E, Pagliara M, Dall´Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passerti M, Reaven G. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med. 1989; 320:703-6.

20- Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol. 1993; 137: 959-65.

21- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412-9.

22- Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna RC, Muggeo M. Prevalence of insulin resistance in metabolic disorders. The Bruneck Study. Diabetes. 1998; 47: 1643-9.

23- De Fronzo, Simon D, Ferranini E. Hepatic and peripheral insulin resistance: a common feature of type 2 and type 1 diabetes mellitus. Diabetologia. 1982; 23: 313-9.

24- Willians KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can Clinical Factors Estimulate Insulin resistance in type 1 Diabetes? Diabetes 49: 626-632, 2000.

25- Olson JC, Erbey JR, Forrest KYZ, Williams K, Becker DJ, Orchard TJ. Glycemia (or, in women, estimated glucose disposal rate) predict lower extremity arterial disease events in type 1 diabetes. Metabolism. 2002; 51: 248-54.

26- Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: a 12 – year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate. The Pittsburgh Epidemiology of Diabetes Complications study experience. Diabetes Care. 2007; 30: 1248-54.

27- Consensus development on the diagnosis of coronary heart disease in people with diabetes: 10-11 February 1998. Miami, Florida: American Diabetes Association. Diabetes Care.1998; 21: 1551-9.

28- Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. Factors influencing the prognosis. Diabetologia. 1978; 14: 371-7.

29- Krolewski AS, Kosinski EJ, Warram JH: Magnitude and determinants of coronary artery disease in juvenile-onset insulin-dependent diabetes. Am J Cardiol. 1987; 59: 750-5.

30- Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. Am J Public Health. 1991; 81: 1158-62.

31- Soedamah-Muthu SS, Fuler JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High Risk of Cardiovascular Disease in Patients with Type 1 Diabetes in the U.K. A cohort study using the General Practice Research Database. Diabetes Care 29: 798-804, 2006

32- Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Bingley PJ, Patterson CC. Mortality from heart disease in a cohort of 23.000 patients with insulin-treted diabetes. Diabetologia. 2003; 46: 760-5.

33- McGill HC, McMahan CA, Zieske AW, Tracy RE, Malcolm GT, Herderick BS, Strong JP: Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. Circulation. 2000; 102: 374-9.

34- Tzcu EM, Kapadia SR, Tutar E, Ziada K, Hobbs R, Mccarthy PM, Young JB, Nissen SE. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults. Circulation. 2001; 103: 2705-10.

35- Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care. 2006; 29: 2528-38.

36- Price CT, Becker DJ, Costacou T, Miller RG, Orchard TJ. Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC). Diabetologia. 2007; 50: 2280-8.

37- Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, Moss SE, Reinke JO. Cardiovascular disease, mortality, and retinal microvascular characteristics

in type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Intern Med. 2004; 164: 1917-24.

38- Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. Br Med J. 1996; 313: 779-84.

39- Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis. 2000; 148: 159-69.

40- Lehto S, Ronnemaa T, Pyorata K, Laako M. Poor glycaemic control predicts coronary heart disease events in patients with type 1 diabetes without nephopathy. Arterioscler Thromb Vasc Biol. 1999; 19: 1014-19.

41- Stettler C, Allemann S, Juni P. Glycaemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J. 2006; 152: 27-38.

42- The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005: 353: 2643-53.

43- De BG, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003; 24: 1601-10.

44- Kim WY, Astrup AS, Stuber M, Tarnow L, Falk E, Botnar RM et al. Subclinical Coronary and Aortic Atherosclerosis Detected by Magnetic Resonance Imaging in Type 1 Diabetes with and without Diabetic Nephropathy. Circulation. 2007; 115: 228-35.

45- Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barret EJ. Screening for coronary artery disease in patients with diabetes. Diabetes Care. 2007; 30: 2729-36.

46- Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G, Manes C, Fuller JH; EURODIAB Prospective Complications Study Group. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. Diabetes Care. 2004; 27: 530-7.

47- Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis in highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol. 1998; 31: 126-33.

48- Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol. 2007; 49: 1860-70.

49- Dabalea D, Kinney G, Snell-Bergeon JK, Hokanson JE, Eckel RH, Ehrlich J, Garg S, Hamman RF, Rewers M. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. Diabetes. 2003; 52: 2833-39.

50- Colhoun HM, Rubens MB, Underwood SR, Fuller JH. The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. J Am Coll Cardiol. 2000; 36: 2160-67.

51- Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with type 1 diabetes. Diabetes. 2000; 49: 1571-78.

52- Davis TME, Bruce DG, Davis WA: Prevalence and prognostic implications of the metabolic syndrome in community-based patients with type 1 diabetes: The Fremantle Diabetes Study. Diabetes Res Clin Pract. 2007; 78: 412-7.

53- Metascreen Writing Committee. The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes. Diabetes Care. 2006; 29: 2701-7.

54- Chatuverdi N, Sjoelie AK, Porta M, Aldington SJ, fuller JH, Songigi M, Kohner EM The EURODIAB Prospective Complications Study Group. Markers of Insulin Resistance are Strong Risk Factors for Retinopathy Incidence in Type 1 Diabetes. The EURODIAB Prospective Complications Study. Diabetes Care. 2001; 24: 284-9.

55- Orchard TJ, Chang Y-F, Ferrel RE, Petro N, Ellis DE. Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. Kidney Int. 2002; 62: 963-70.

56- Svensson M, Yu ZW, Eriksson JW. A small reduction in glomerular filtration is accompanied by insulin resistance in type I diabetes patients with diabetic nephrophathy. Eur J Clin Invest. 2002; 32:100-9.

57- Ekstrand AV, Groop P-H, Gronhagen-Riska C. Insulin resistance precedes microalbuminuria in patients with insulin-dependent diabetes mellitus. Nephrol Dial Transplant. 1998; 13: 3079-83.

58- Hasslacher C, Stech W, Wahl P, Ritz E. Blood pressure for nephropathy in type 1 (insulin-dependents) diabetes. Diabetologia. 1985; 28: 6-11.

59- Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes. “Double diabetes” in the Diabetes Control and Complications Trial. Diabetes Care. 2007; 30: 707-12.

60- Sibley SD, Palmer JP, Hirsch IB, Brunzell JD. Visceral obesity, hepatic lipase activity, and dyslipidemia in type 1 diabetes. J Clin Endocrinol Metab. 2003; 88: 3379-84.

61- Kabadi UM, Vora A, kabadi M. Hyperinsulinemia and central adiposity. Diabetes Care. 2000; 23: 1024-25.

62- Bujalska IJ, Kumar S, Stewart PM. Does central obesity reflect “Cushing’s disease of the omentum”? Lancet. 1997; 349: 1210-13.

63- De Block CE, De Leeuw IH, Van Gaal LF. Impact of overweight on chronic microvascular complications in type 1 diabetic patients. Diabetes Care. 2005; 28: 1649-55.

64- Strowic SM, Raskin P. The effect of rosiglitazone on overweight subjects with type 1 diabetes. Diabetes Care. 2005; 28: 1562-67.

65- Pagano G, Tagliaferro V, Carta Q, Caselle MT, Bozzo C, Vitelli F, Trovati M, Cocuzza E. Metformin reduces insulin requirement in type 1 (insulin-dependent) diabetes. Diabetologia. 1983; 24: 351-4.

66- Meyer L, Bohme P, Delbachian I, Lehert P, Cugnardey N, Drouin P, Guerci B. The benefits of metformin therapy during continuos subcutaneous insulin infusion treatment of type 1 diabetic patients. Diabetes Care. 2002; 25: 2153-8.

67- Sarnblad S, Kroon M, Aman J. Metformin s additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity. Eur J Endocrinol. 2003; 149: 323-9.

68- Hamilton J, Curnmings E, Zdravkovic V, Finegood D, Daneman D. Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. Diabetes Care. 2003; 26: 138-43.

69- Idzior-Walus B, Mattock MB, Solnica B, Stevens L, Fuller JH and the EURODIAB IDDM Complications Study Group. Factors associated with plasma lipids and lipoproteins in type 1 diabetes mellitus: the EURODIAB IDDM Complications Study. Diabetic Medicine. 2001; 18: 786-96.

70- Rodrigues TC. Síndrome Metabólica, Cálcio Coronário e Homeostase Pressórica em Pacientes com Diabetes Melito Tipo 1. [Tese]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2008.

Tabela 1: Critérios diagnósticos da SM segundo as 3 definições mais utilizadas: OMS, NCEP-ATP III e IDF.

OMS exige a presença de resistência à ação da insulina ou de hiperglicemia e mais dois outros componentes:		**Níveis**
Presença de hipertensão ou uso de anti-hipertensivos		≥ 140/90 mmHg
IMC ≥ 30 Kg/m^2 e/ou relação cintura/quadril	Masculino	> 0,90
	Feminino	> 0,85
Presença de micro ou macroalbuminúria		> 20 µg/min
Triglicerídeos		> 150 mg/dl
HDL colesterol	Masculino	< 35 mg/dl
	Feminino	< 39 mg/dl
Glicemia		≥ 110 mg/dl
O NCEP-ATP III exige a presença de 3 dos seguintes componentes:		**Níveis**
Pressão arterial		≥ 130 mmHg PAS ou ≥ 85 mmHg PAD
Circunferência abdominal	Masculino	> 102 cm
	Feminino	> 88 cm
Triglicerídeos		> 150 mg/dl
HDL colesterol	Masculino	< 40mg/dl
	Feminino	< 50 mg/dl
Glicemia		≥ 100 mg/dl
O IDF exige a presença de obesidade abdominal e outros 2 componentes:		**Níveis**
Presença obrigatória de obesidade abdominal		
Para europeus e árabes	Masculino	≥ 94 cm
	Feminino	≥ 80 cm
Para asiáticos, latinos da América central e do sul	Masculino	≥ 90cm
	Feminino	≥ 80 cm
Pressão arterial		≥ 130 mmHg PAS ou ≥ 85 mmHg PAD
Triglicerídeos		> 150 mg/dl
HDL colesterol	Masculino	< 40mg/dl

	Feminino	< 50 mg/dl
Glicemia		≥ 100 mg/dl

Capítulo 2

Metabolic Syndrome, Hypertension and Microvascular Complications and Coronary Calcium Score in Type 1 Diabetes

Short running title: metabolic syndrome and chronic complications in type 1 diabetes

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Abstract

OBJECTIVE: To evaluate the association of metabolic syndrome (MetS) or its individual components with microvascular complications and coronary artery calcification in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS: All consecutive type 1 diabetes patients without renal replacement therapy or previous renal transplant were assessed for the presence of MetS (NCEP criteria), retinopathy (direct and indirect fundoscopy after mydriasis), urinary albumin excretion rate (UAER, immunoturbidimetry). A subset of 100 patients selected based on the absence of known cardiovascular disease and more than 5 years duration of diabetes also underwent coronary artery calcium (CAC) score measurement.

RESULTS: MetS was observed in 35 out of 255 (15.7%) patients. Patients with MetS had more frequently retinopathy (n = 24 [68%]), nephropathy (UAER >20µg/dl, n = 23 [66.7%]) and presence of CAC (n = 19 [54%]). In a multiple logistic regression analysis MetS remained significantly associated with nephropathy [OR: 5.83 (95% CI 2.27- 14.96), P < 0.001] and presence of CAC [OR: 7.04 (95% CI 1.0 – 51.08), P = 0.05] only in women and not with retinopathy. Replacing MetS by its components revealed that hypertension had a greater association with the presence of retinopathy (OR: 4.82 [95% CI 1.69 – 13.7], P =

0.003), nephropathy (OR: 10.19 [95% CI 2.27 – 45.71], P = 0.002) and CAC in women (OR: 10.32 [CI 95% 1.31 – 80.9], P = 0.02).

CONCLUSIONS: Hypertension is the MetS component that has a greater association with retinopathy, nephropathy and CAC in women than MetS itself.

Keywords: metabolic syndrome, hypertension, microvascular complications, coronary arterial calcification, type 1 diabetes

The presence of metabolic syndrome (MetS) has been considered a risk factor for cardiovascular disease and early mortality in non diabetic subjects (1, 2). MetS has been observed in 80 to 90% of patients with type 2 diabetes and it is associated not only with macrovascular disease but also with microvascular complications (3). However, the role of MetS besides its components as an independent risk factor for the development of cardiovascular events has been questioned (4). It is particularly complex to analyze this aspect in patients with type 2 diabetes since the vast majority of them present MetS (5) already years before the diagnosis of diabetes (6). Considering that MetS has been observed in 12% to 42% of patients with type 1 diabetes (7, 8, 9) and its prevalence increases progressively throughout the duration of diabetes (10), it might be hypothesized that it represents an additional risk factor for the development of macro- and microvascular complications in patients with type 1 diabetes. Few studies have addressed this aspect and the results are still contradictory, probably due to different study design and ethnicity factors. In the FinnDiane study the type 1 diabetic patients with MetS had a 3.75-fold odds ratio for diabetic nephropathy (7). On the other hand, in two prospective studies the individual components are a better predictive factor than the presence of MetS (8,11), or its presence did not add significant prognostic predictive value to conventional vascular risk factors (9) or insulin resistance index (10).

Therefore, the aim of this study was to evaluate whether MetS or its individual components are associated with the presence of diabetic retinopathy and nephropathy and subclinical atherosclerosis assessed by Coronary Artery Calcification (CAC) in a cohort of type 1 diabetic patients.

Research Design and Methods

A cross-sectional study was conducted in 255 type 1 diabetic patients, regularly attending the Endocrine Division's outpatient clinic at Hospital de Clínicas de Porto Alegre. Type 1 diabetes was defined based on World Health Organization criteria, i.e., age <40 years at onset of diabetes, a previous episode of ketoacidosis or documented ketonuria, and mandatory use of insulin for survival. Patients with end-stage renal disease [(ESRD), in a dialysis program or with kidney transplantation] were excluded. A sample of 100 patients with type 1 diabetes selected based on the absence of known cardiovascular disease and more than 5 years duration of diabetes underwent CAC score measurement. The Ethics Committee of the hospital approved the project, and written informed consent was obtained from all patients.

Patient evaluation

Patients answered a standardized questionnaire, underwent a complete physical examination that included measurement of waist circumference (mid axillary line midway between the highest point of the iliac crest and lowest point of the costal margin), height, weight in light clothes and without shoes, and BMI was calculated [weight (kg)/height^2 (m)]. Blood pressure was measured twice in a sitting position after 10 min rest with a standard 12.5 cm Hg cuff mercury sphygmomanometer (Kortokoff phase I and IV). The mean of 2 measures was used for analysis.

Retinopathy was assessed by direct and indirect ophthalmoscopy after mydriasis by the same ophthalmologist, and for the purpose of this study, patients were classified only according to the presence or absence of any degree of diabetic retinopathy (DR). The presence of diabetic nephropathy (DN) was defined according to urinary albumin excretion rate (UAER), measured in two 24-h sterile urine collections, 3-monthly intervals. Patients

with microalbuminuria (UAER >20 and <200 μg/min) and macroalbuminuria (UAER >200 μg/min) were analyzed as a group with DN. The diagnosis of cardiovascular disease was established by the presence of a positive medical history of myocardial infarction, angina, coronary artery bypass graft or stroke.

The presence of MetS was determined according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), as modified by the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (12). The NCEP requires that the patients have three or more: waist circumference ≥102 cm in men and ≥88 cm in women, triglycerides ≥150 mg/dl, HDL <40 mg/dl in men and <50mg/dl in women, blood pressure ≥135/85 mm Hg or be using antihypertensive drugs and fasting glucose ≥ 100mg/dl.

CAC was measured using a multidetector computed tomography system that acquired 64 simultaneous 2.5-mm slices for each cardiac cycle with prospective ECG-triggered scan acquisition at 60% of the RR interval in a sequential or axial scan mode (Siemens Sensation 64 Cardiac). All scans were analyzed for the presence of CAC on an offline workstation (Circulation, Siemens). A calcified lesion was defined as an area with a CT attenuation >130 HU. The Agatston score was calculated by multiplying the area of each lesion with a weighted CT attenuation score depending on the maximal CT attenuation (HU) within the lesion. The radiologist reading CT scans was unaware of the clinical data.

Laboratory Measurements

UAER was measured by immunoturbidimetry (Microal; Ames-Bayer, Tarrytown, NY) (intra-and interassay coefficients variation of 4.5 and 11%, respectively), A1c by a high-performance liquid chromatography system (reference range 4-6%; Merck-Hitachi

9100), fasting plasma glucose by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica), and the lipid profile by a colorimetric method. Serum creatinine was measured by the Jaffé method and the glomerular filtration rate (GFR) was estimated by using the formula of the Modification of Diet in Renal Disease Study (13): 186 x [serum creatinine $^{-1.154}$ x age$^{-0.203}$ x (0.742, if female) x (1.210, if of African ethnicity)]. Estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, was calculated based on a regression equation: eGDR (mg.kg^{-1}.min^{-1}) = 24.4 – 12.97 (waist/hip ratio) – 3.39 x (presence or absence of hypertension) – 0.60 x (Hb_{A1c}). This equation was derived from hyperinsulinemic-euglycemic clamp studies, and has been validated (14).

Statistical analysis

Student's t-test was used for continuous variables and the ^{2} test was used for categorical variables. Mann-Whitney U test was used to compare CAC scores. Multiple logistic regression analyses were performed with the presence of diabetic retinopathy, diabetic nephropathy or CAC (presence or absence) as the dependent variables and MetS, current smoking habit, diabetes duration and A1c test as independent variables. Alternative models were built replacing MetS with its individual components (hypertension, abdominal circumference, HDL and triglycerides) as independent variables. Data were expressed as mean ± S.D., except for UAER, triglycerides, eGDR and CAC which were expressed as median and range. Variables with non normal distribution were log-transformed for analyses. P value <0.05 was considered to be significant.

Results

The prevalence of MetS was 15.7% (35 / 255) and there was no difference between men (11%) (15/121) and women (16%) (20/134). The clinical and laboratory characteristics of patients with and without MetS are described in the Table 1. Patients with MetS were

older and had a longer duration of diabetes, were more frequently white and are current smokers. The eGDR was lower suggesting increased insulin resistance. Neither glycemic control nor mean dose of insulin used were different. As expected, patients with MetS had higher BMI, waist circumference, BP levels, and the lipid profile was less favorable than patients without MetS. Patients with MetS also had more microvascular complications including retinopathy and nephropathy. When all patients were classified according to the stage of diabetic nephropathy in normo-, micro- or macroalbuminuria, the prevalence of MetS increased progressively from 7% in normo- to 23% in micro- and 50% in macroalbuminuric patients ($P < 0.001$). Moreover, the log eGDR had a significant correlation with eGFR ($r = 0.18$, $P = 0.012$) and with log UAE ($r = -0.37$, $P < 0.001$).

In the subset of 100 patients who underwent CAC measurement, higher CAC score values ($P=0.01$) were observed in patients with MetS [2.0 (0.0 - 1364), n = 19] than in patients without MetS [0.0 (0.0 - 1410), n = 81], but this difference was significant ($P = 0.001$) only in women [55.10 (0.0 - 1364), n = 8 with MetS vs. 0.0 (0.0 – 70.6), n=34 without MetS] and not in men [0.0 (0.0 - 415), n = 11 with MetS vs. 0.0 (0.0 - 1410), n = 47 without MetS], (Figure 1).

To verify whether MetS was associated with diabetic complications independently of other possible confounding factors, multiple logistic regressions analyses were performed with DR, DN and CAC as dependent variables. Diabetes duration, smoking, gender and A1c were entered as independent variables. MetS [OR: 5.83 (95% CI 2.27-14.96), $P < 0.001$], A1c [OR 1.44 (95% CI 1.18 – 1.76), $P < 0.001$] and diabetes duration [OR 1.04 (1.0 – 1.09), $P = 0.025$] remained significantly associated with nephropathy.MetS had a borderline statistical significance with the presence of CAC [OR: 7.04 (95% CI 1.0 – 51.08), $P = 0.05$] only in women. MetS did not remain significantly associated with

retinopathy. The presence of retinopathy was associated only with the diabetes duration [OR: 1.17 (95% CI 1.10 – 1.23), P <0.001].

Multiple regression analysis was also performed replacing MetS by its individual components (waist circumference, log-triglycerides, HDL cholesterol and presence of hypertension), as independent variables. Nephropathy was associated with A1c [OR: 1.68, (95% CI 1.10 – 2.57), P = 0.016] and presence of hypertension [OR: 10.19 (95% CI 2.27 – 45.71), P = 0.002]. Retinopathy was associated with diabetes duration [OR: 1.14 (95% CI 1.07 – 1.21), P <0.001] and presence of hypertension [OR 4.82 (95% CI 1.69 – 13.7), P = 0.003]. CAC, in women, was associated only with the presence of hypertension [OR: 10.32 (95% CI 1.31 – 80.9), P = 0.02] and in men, only with age [OR: 1.16 (95% CI 1.5 – 1.28), P = 0.004].

Conclusions

In this sample of patients with type 1 diabetes the presence of MetS was significantly associated only with diabetic nephropathy and with the presence of CAC in women, although the statistical significance was borderline. Hypertension was the MetS component that had a greater association with retinopathy, nephropathy and presence of CAC in women.

The prevalence of MetS observed in this study (15.7%) was similar to the 12.5% reported in the follow-up study of the DCCT cohort (9) also defined by NCEP criteria. However, in the FinnDiane study, the prevalence of MetS in type 1 diabetic patients was higher, around 40% (7), but interestingly the age range and insulin resistance index (eGDR: 4.8 $mg.kg^{-1}.min^{-1}$) were very similar to those observed in the present study (4.9 $mg.kg^{-1}.min^{-1}$). This discrepancy might be explained by the inclusion of patients with ESRD in dialysis or with kidney transplant in the FinnDiane study and not in the present study, and the

prevalence of MetS increases according to the degree of renal involvement (7). In fact, we observed that the prevalence of MetS increased progressively from patients with normo- to micro- and macroalbuminuria.

The association of MetS with microvascular complications (retinopathy and nephropathy) had already been demonstrated in type 2 diabetic patients (1, 3, 6) but in patients with type 1 diabetes only diabetic nephropathy was significantly associated with MetS (7, 8). The association of MetS or insulin resistance with diabetic nephropathy in patients with type 1 diabetes was already described many years ago (15). In the DCCT cohort the eGDR index at baseline was significantly associated with a subsequent increased risk for development of both micro- and macrovascular complications (10). In the present study a significant correlation was observed of the eGDR with GFR and UAE, reinforcing the role of insulin resistance in the development of DN. In the FinnDiane study there was a significant association between MetS and albuminuria, and the prevalence of MetS increased with the progression of nephropathy and worsening of glycemic control. The summation of the data presented above supports the role of insulin resistance and MetS in the development of complications, especially nephropathy in patients with type 1 diabetes as was also demonstrated in the present study.

The observed association of MetS and CAC in women in the present study, as far as we know, had not been previously reported. This observation is consistent with the association of MetS with subclinical atherosclerosis previously reported in non-diabetic individuals and type 2 diabetic patients (16, 17). In the Bogalusa Heart Study the carotid intima-media thickness was significantly higher in younger adults with MetS than in those without MetS (16). The prevalence of CAC was higher in individuals with MetS or diabetes in a cohort of asymptomatic patients with ages from 20 to 79 years (17). In patients with

type 1 diabetes, even after controlling for the traditional cardiovascular risk factors, there was a three-fold increase in the prevalence of coronary calcification in women as compared to men (18). Women with diabetes are more susceptible to the development of CHD (19) and therefore, we might suggest that the increased CAC observed in women in the present study is probably related to a more pronounced effect of MetS in women.

The presence of hypertension was the individual component of MetS which presented a greater association with retinopathy and nephropathy in all patients and with CAC only in women than MetS itself. It is well known that hypertension is a major risk factor for the development of micro- and macrovascular complications in patients with type 1 diabetes (20, 21, 22). In fact, we have previously demonstrated that blood pressure levels at the upper limit of the normal range are already a risk factor for the development DR in a prospective study of a cohort of normotensive type 1 diabetic patients (23). A study that evaluated the progression of CAC in diabetic and non-diabetics patients, showed that the presence of both diabetes and hypertension were the best predictors of progression of CAC (24).

In conclusion, patients with type 1 diabetes and MetS had more frequently diabetic nephropathy and CAC but hypertension was the MetS component with a greater association with retinopathy, nephropathy and CAC.

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References

1- Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissen M, Taskinen M-R, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24: 683-689, 2001

2- Lakka H-M, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288: 2709-2716, 2002

3- Costa LA, Canani LH, Lisbôa HR, Tres GS, Gross JL: Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in Type 2 diabetes**.** *Diabet Med* 21:252-5, 2004

4- Gale EA: The myth of the metabolic syndrome. *Diabetologia* 48:1679-83, 2005

5- Bonora E, Targher G, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Gemma L, Santi L, Bonadonna RC, Muggeo M: The metabolic syndrome is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabet Med* 21: 52-58, 2004

6- The Metascreen Writing Committee: The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes: Results from Metascreen, a multicenter diabetes clinic–based survey. *Diabetes Care* 29: 2701-2707, 2006

7- Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Wadén J, Rónnback M, Rosengard-Barlund M, Taskinen M-R, Groop P-H: Metabolic syndrome in type 1 diabetes. Association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care* 28: 2019-2024, 2005

8- Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: a 12 – year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate. The Pittsburgh Epidemiology of Diabetes Complications study experience. *Diabetes Care* 30: 1248-1254, 2007

9- Davis TME, Bruce DG, Davis WA: Prevalence and prognostic implications of the metabolic syndrome in community-based patients with type 1 diabetes: The Fremantle Diabetes Study. *Diabetes Res Clin Pract* 78: 412-417, 2007

10- Kilpatrick ES, Rigby AS, Atkin SL: Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes. *Diabetes Care* 30: 707- 712, 2007

11- Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KYZ, Kinder LSK, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes. 10 years follow-up data from the Pittsburgh epidemiology of diabetes complications study. *Diabetes Care* 26: 1374-1379, 2003

12- Grundy SM, Cleeman JL, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 25: 2735-2752, 2005

13- Levey AS, Coresh J, balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G: National Kidney Foundation practice guidelines for chronic kidney: evaluation, classification, and stratification. *Ann Intern Med* 139: 137-147, 2003

14- Williams KV, Erbey JR, Becker D, Arsianian S, Orchard TJ: Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 49: 626-632, 2000

15- Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti G: Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. *Lancet* 342 : 883-887, 1993

16- Tzou W, Douglas P, Srinivasan SR, Bond G, Tang R, Chen W, Berenson GS, Stein JH: Increased subclinical atherosclerosis in young adults with metabolic syndrome. The Bogalusa Heart Study. *J Am Coll Cardiol* 46: 457-463, 2005

17- Wong ND, Sciammarella MG, Polk D, Gallagher A, Miranda-Peats L, Whitcomb BS, Hachamovitch R, Friedman JD, Hayes S, Berman DS: The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol* 41: 1547-1553, 2003

18- Calhoun HM, Rubens MB, Underwood SR, Fuller JH: The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. *J Am Coll Cardiol* 36: 2160-2061, 2000

19- Krolewski AS, Kosinski EJ, Warram JH: Magnitude and determinants of coronary artery disease in juvenile-onset insulin-dependent diabetes. *Am J Cardiol* 59: 750-755, 1987

20- Sjolie AK, Stephenson J, Aldington S, Kohner E, Janka H, Stevens L, Fuller J: Retinopathy and vision loss in insulin dependent diabetes in Europe: the EURODIAB IDDM Complications Study. *Ophthalmology* 104: 252-260, 1997

21- Mogensen CE: Progression of nephropathy in long-term diabetics with proteinuria and the effect of initial anti-hypertensive treatment. *Scand Clin Lab Invest* 36: 383-388, 1976

22- Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ: Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis* 148: 159-169, 2000

23- Rodrigues TC, Pecis M, Azevedo MJ, Esteves JF, Gross JL: Ambulatory Blood Pressure Monitoring and progression of retinopathy in normotensive, normoalbuminuric type 1 diabetic patients: A 6 - year follow-up study. *Diabetes Res Clin Pract* 74: 135-140, 2006

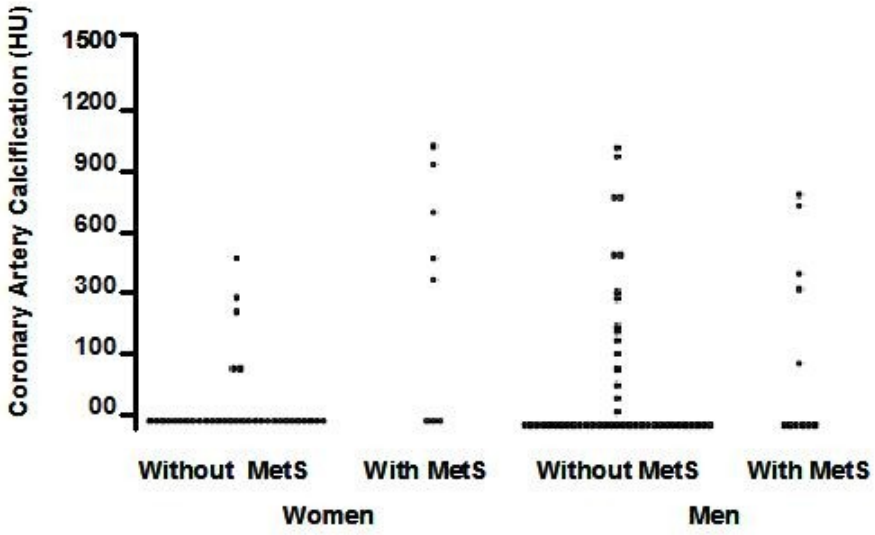
24- Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M: Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. *Hypertension* 46: 238 - 243, 2005

Table 1: Descriptive data for patients with and without metabolic syndrome

	With Metabolic Syndrome n = 35	**Without Metabolic Syndrome n = 220**	**P**
Men n (%)	15 (43)	119 (54)	0.21
Age (years)	41.5 ± 12	33.7 ± 10	0.001
Age of onset (years)	19.4 ± 10	18.4 ± 10	0.59
Diabetes duration (years)	22.0 ± 12	15.3 ± 8	<0.001
Ethnicity (white) n (%)	33 (94)	196 (89)	0.35
Waist circumference (cm)			
Men	93.6 ± 9	82.5 ± 7	0.001
Women	89.5 ± 5	78.7 ± 8	<0.001
BMI (kg/m^2)	27.3 ± 3	24.0 ± 3	<0.001
Systolic blood pressure (mmHg)	134.3 ± 15	119.2 ± 15	<0.001
Diastolic blood pressure (mmHg)	83.7 ± 10	76.3 ± 10	<0.001
Hypertension n (%)	30 (86)	41 (18.6)	<0.001
Current smoking n (%)	9 (27)	31 (14)	<0.001
Insulin dose/kg (U/kg)	0.74 ± 0.24	0.74 ± 0.24	0.90
Total cholesterol (mg/dl)	188.5 ± 52	174.7 ± 40	0.07
HDL cholesterol (mg/dl)	51.0 ± 15	59.0 ± 15	0.006
LDL cholesterol (mg/dl)	108.2 ± 40	100.0 ± 34	0.20
Triglycerides (mg/dl)	121 (47-436)	71 (22-706)	<0.001
A1c (%)	8.6 ± 2	8.5 ± 2	0.80
eGDR ($mg.kg^{-1}.min^{-1}$)	4.9 (2.0-10.6)	8.7 (2.2-11.6)	<0.001
eGFR (ml/min per $1.73m^2$)	73 ± 41	88 ± 28	0.04
Diabetic retinopathy n (%)	24 (68)	94 (43)	0.01
Diabetic nephropathy n (%)	23 (66.7)	53 (24)	<0.001

Data are means ± SD, median (range) or %. BMI: body mass index, GDR: glucose disposal rate, GFR: glomerular filtration rate

Figure 1: Coronary artery calcification in women and men marked according to the presence or absence of metabolic syndrome.



CAPÌTULO 3

Coronary Artery Calcification in Women with Type 1 Diabetes is Associated with Insulin Resistance Index

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Abstract

OBJECTIVE: To evaluate the possible risk factors associated with the presence of coronary artery calcium (CAC) in patients with type 1 diabetes. **METHODS:** This cross sectional study was conducted in 100 consecutive type 1 diabetes patients attending the outpatient clinic of a university hospital with >18 years and absence of known cardiovascular disease and more than 5 years duration of diabetes without renal replacement therapy or previous renal transplant. CAC score was measured by using multidetector computed tomography (Siemens Sensation 64 Cardiac) and the Agatston scoring method. **RESULTS**: Presence of CAC was observed in 31 out of 100 patients. Patients with CAC were older, had a longer duration of diabetes, were more frequently hypertensive, had higher waist/hip ratio, metabolic syndrome (MetS) and more frequently had diabetic retinopathy. The eGDR was lower, suggesting increased insulin resistance. In men, in a multiple logistic regression analysis only age was significantly associated with CAC [OR: 1.15 (95% CI: 1.06 – 1.25), P=0.001]. In women, only eGDR remained associated with CAC [OR: 0.34 (95% CI: 0.12 – 0.92), P = 0.03]. **CONCLUSIONS:** CAC in patients with type 1 diabetes was associated with age in men and with an index of insulin resistance (eGDR) in women.

Keywords: Coronary Artery Calcification, Type 1 Diabetes, Insulin Resistance

Patients with type 1 diabetes are at increased risk for coronary artery disease (CAD) (1) and this might occur earlier in life (2). Detection of coronary artery calcification (CAC) has been increasingly used as a new tool to assess CAD and to predict coronary events beyond standard risk factors (3). The amount of coronary artery calcification (CAC) has an excellent correlation ($r > 0.90$) with coronary atherosclerotic plaque burden (4) and presence of CAC is correlated with CAD in both men and women (5). Patients with diabetes had higher CAC scores than non-diabetic individuals (6) but the factors associated with the presence of CAC in patients with type 1 diabetes are still not yet fully defined. Therefore, the aim of this study was to evaluate the risk factors associated with the presence of CAC in a sample of type 1 diabetic patients.

We performed a cross-sectional study in consecutive type 1 diabetes patients (WHO criteria), attending the Endocrine Division's outpatient clinic at Hospital de Clínicas de Porto Alegre. Inclusion criteria were age >18 years, at least 5 years duration of diabetes and absence of end stage renal disease (dialysis or renal transplant) and known cardiovascular disease defined based on a normal resting ECG and a negative medical history of myocardial infarction, angina, intermittent claudication, coronary artery revascularization procedure or stroke. The Ethics Committee of the Hospital approved this study, and informed written consent was obtained from all patients.

Patients underwent an interview and clinical examination to record demographic and anthropometric data, as previously described (7). Retinopathy was assessed by direct and indirect ophthalmoscopy after mydriasis by the same ophthalmologist, and for the purpose of this study patients were classified only according to the presence or absence of any degree of diabetic retinopathy (DR). Patients with microalbuminuria [urinary albumin excretion rate (UAER) >20 and <200 μg/min)] and macroalbuminuria (UAER >200

µg/min) were analyzed as a group with diabetic nephropathy (DN). Metabolic syndrome (MetS) was classified by NCEP criteria (8). UAER was measured by immunoturbidimetry (Microal; Ames-Bayer, Tarrytown, NY, intra-and interassay coefficients variation of 4.5 and 11%, respectively). A1c was measured by a high-performance liquid chromatography system (normal range 4-6%; Merck-Hitachi 9100). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica), creatinine by the Jaffé method and the glomerular filtration rate (GFR) was estimated using the formula of the Modification of Diet in Renal Disease Study (9). The lipid profile was measured by a colorimetric method, high sensitivity C reactive-protein (CRP) by nephelometry and fibrinogen by coagulometric method. Estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, was calculated using regression equation (involving HbA1c, waist-to-hip ratio and hypertension) derived from hyperinsulinemic-euglycemic clamp studies (10). CAC was measured using a multidetector computed tomography system that acquired 64 simultaneous 2.5-mm slices for each cardiac cycle with prospective ECG-triggered scan acquisition at 60% of the RR interval in a sequential or axial scan mode (Siemens Sensation 64 Cardiac). All scans were analyzed for the presence of CAC on an offline workstation (Circulation, Siemens). A calcified lesion was defined as an area with CT attenuation >130 HU. The Agatston score was calculated by multiplying the area of each lesion by a weighted CT attenuation score depending on the maximal CT attenuation (HU) within the lesion. The radiologist reading CT scans was unaware of the clinical data.

Student's t-test and the $^{2}\chi$ test were used to compare clinical and laboratory data. Pearson correlation was used. Data with a normal distribution were expressed as mean ± S.D, and quantitative variables without a normal distribution (UAER, CRP, triglycerides, eGDR, fibrinogen and CAC) were log transformed before analysis and expressed as median

and range. Models of multiple linear regressions and multiple logistic regressions analyses were performed with the amount or presence of CAC as a dependent variable. P values < 0.05 (two tailed) in the univariate analysis were considered to be significant.

Of 100 patients evaluated, 31 presented CAC. Clinical and laboratory data were described in Table 1 and Table 2 respectively. Patients with presence of CAC were older (all, except 2, were >35 years old), had a longer duration of diabetes, were more frequently hypertensive, and had higher waist/hip ratio (WHR), higher prevalence of MetS and DR. Fibrinogen level was higher.The eGDR was lower suggesting increased insulin resistance. Lipid profile, glycemic control and the mean dose of insulin used were not different between the groups.

The proportion of patients with CAC was not different between men (21/58 = 36%) and women (10/32 = 31%, P = 0.20), as well as the amount of CAC (P = 0.22). Age and BMI were the only factors associated with the presence of CAC in men and, in a multiple logistic analysis only age remained associated with CAC [OR: 1.15 (95% CI: 1.06 – 1.25), P=0.001]. In men with the presence of CAC, the amount of calcium in the coronaries (Hounsefield units) had a significant correlation with age (r = 0.60, P <0.001), diabetes duration (r = 0.58, P <0.001), eGDR (r = - 0.31, P = 0.02) and eGFR (r = - 0.26, P = 0.04). UAER did not correlate with the amount of CAC. In a multiple regression linear analysis with the amount of CAC as dependent variable only age remained significantly associated (R = 0.594, R_a^2 = 0.325, P <0.001) and diabetes duration, eGDR and eGFR were excluded from the model.

Women with CAC were older and and more frequently had hypertension, longer duration of diabetes, higher WHR, and the eGDR and eGFR were lower than in women without CAC. MetS, DR and DN were also more prevalent in the women with CAC. To

analyze the possible association between the cardiovascular risk factors and the presence of CAC, multiple logistic regression analyzes were performed with the presence of CAC as dependent variable. Age or diabetes duration, presence of DR, eGDR and GFR or presence of DN were used as independents variables, and only eGDR remained significantly associated with CAC [OR: 0.34 (95% CI: 0.12 – 0.92), P = 0.03]. Replacing eGDR by systolic blood pressure and WHR, none remained associated with the presence of CAC.

The amount of CAC in women had a significant correlation with age (r = 0.43, P = 0.005), diabetes duration (r = 0.51, P = 0.001), WHR (r = 0.47, P = 0.001), systolic blood pressure (r = 0.38, P = 0.01), eGDR (r = - 0.70, P <0.001), fibrinogen level (r = 0.37, P = 0.04) and eGFR (r = - 0.40, P = 0.009). There was no correlation between CAC and UAE. In a multiple regression linear analysis with the amount of CAC as dependent variable and age or diabetes duration, eGFR and eGDR as independent variables, only eGDR and diabetes duration remained significantly associated (R = 0.800, R_a^2 = 0.610, P <0.001), age and GFR were excluded from the model. In additional models, with diabetes duration, WHR, systolic blood pressure and eGFR as independent variables, only diabetes duration, WHR and eGFR remained associated with the outcome (R = 0.689, R_a^2 = 0.416, P<0.001).

In the present study there was no difference in the proportion of men and women with the presence of CAC. Moreover, the risk factors associated with the presence and amount of CAC were different in women and men with type 1 diabetes. In men, only age was related to CAC, but in women CAC was associated with indices of insulin resistance and MetS. It has been consistently shown that the association of diabetes with CAD is stronger in women than in men; therefore the presence of diabetes may reduce the gender gap in risk for CAD (11). Actually, the amount and the proportion of CAC in women and men were not different. In individuals without diabetes, women usually have a lower

prevalence of CAC than men of the same age, and the prevalence of CAC in women is similar to that in men who are a decade younger (3). Therefore, it is currently acknowledged that women with diabetes tend to have a greater burden of CAD risk factors (12). In the present study the components of MetS [(WHR) and an index of insulin resistance (eGDR)] were the factors significantly associated with CAC. Women with type 1 diabetes and presence of CAC had increased central adiposity and had a more android deposition of adipose tissue than control subjects, but this observation was not seen in men with type 1 diabetes (12).

Insulin resistance has been independently associated with CAC in type 1 diabetic patients and might explain the gender difference in CAC in patients with type 1 diabetes and nondiabetic subjects (13, 14, 15, 16). Moreover, recently it has been demonstrated that the index of insulin resistance (eGDR) was associated with CAD only in women with type 1 diabetes (17). The data presented reinforce this concept and suggest that women with diabetes type 1 and with components of MetS should undergo an assessment of CAC already after 35 years of age, and patients with the presence of CAC should be treated more intensively, especially regarding abdominal fat deposition or weight gain.

In conclusion, women with type 1 diabetes are more susceptible to CAD assessed by CAC, probably due to a greater impact of components of MetS and/or insulin resistance on atherosclerosis progression.

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References

1. Laing SP, Swerdlow AJ, Slater DS, Botha JL, Burden AC, Waugh NR, Smith AW, Hill RD, Bingley PJ, Patterson CC, Qiao Z, Keen H. The British Diabetic Association Cohort Study II: Cause specific in patients with insulin-treated diabetes mellitus. *Diabetic Med* 1999; 16: 466-471.

2. Krolewski AS, Kosinski EJ, Warran JH, Leland OS, Busick EJ, Asmal AC, Rand LI, Chrislieb AR, Bradley RF, Kahn CR. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 1987; 59: 750 – 755.

3. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JA, Rader DJ, Rubin GD, Shaw LJ, Wiegers SE. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006 ;114:1761-1791.

4. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis in highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 1998; 31: 126-133.

5. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with type 1 diabetes: a stronger correlate of clinical coronary artery disease in men than in women. *Diabetes* 2000; 49: 1571-1578.

6. Schurgin S, Rich S, Mazzone T. Increased of prevalence coronary artery calcification in patients with diabetes. *Diabetes Care* 2001; 24: 335-338.

7. Rodrigues TC, Pecis M, Azevedo MJ, Esteves JF, Gross JL. Ambulatory Blood Pressure Monitoring and Progression of retinopathy in normotensive, normoalbuminuric type 1 diabetic patient: A 6 - year follow-up study. *Diabetes Res Clin Pract* 2006; 74: 135-140.

8. Grundy SM, Cleeman JL, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005; 25: 2735-2752.

9. Levey AS, Coresh J, balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139: 137-147.

10. Williams KV, Erbey JR, Becker D, Arsianian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 2000; 49: 626-632.

11. Dale AC, Nilsen TI, Vatten L, Midthjell K, Wiseth R. Diabetes mellitus and risk of fatal ischaemic heart disease by gender: 18 years follow-up of 74914 individuals in the HUNT 1 study. *European Heart Journal* 2007; 28, 2924–2929.

12. Barrett-Connor E, Giardina EGV, Gitt AK, Gudat U, Steinberg HO, Tschoepe D. Women and heart disease: The role of diabetes and hyperglycemia. *Arch Intern Med* 2004; 164: 934–942.

13. Dabalea D, Kinney G, Snell-Bergeon JK, Hokanson JE, Eckel RH, Ehrlich J, Garg S, Hamman RF, Rewers M. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. *Diabetes* 2003; 52: 2833-2839.

14. Soedamah- Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K: A

cohort study using the general practice research data base. *Diabetes Care* 2006; 29: 798-804.

15. Olson JC, Erbey JR, Williams KV, Becker DJ, Edmundowicz D, Kelsey SF, Tyrrell KS, Orchard TJ. Subclinical atherosclerosis and estimated glucose disposal rate as predictors of mortality in type 1 diabetes. *Ann Epidemiol* 2002; 5: 331-337.

16. Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY-Z, Smithline Kinder L, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10 year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications study. *Diabetes Care* 2003; 26: 1374-1379.

17. Ruppert K, Roberts MS, Orchard TJ, Zgibor JC. Cardiovascular disease risk prediction in type 1 diabetes: accounting for the differences. *Diabetes Res Clin Pract* 2007; 78: 234-237.

Table 1: Clinical characteristics of patients with and without Coronary Artery Calcification

	All Patients			Men			Women		
	CAC +	CAC –		CAC +	CAC –		CAC +	CAC –	
	n = 31	n = 69	P	n = 21	n = 37	P	n = 10	n = 32	P
Age (years)	47 ± 9	35 ± 9	<0.001	48 ± 10	34 ± 9	<0.001	46 ± 7	37 ± 8	<0.001
Diabetes duration (years)	23 ± 11	16 ± 7	0.003	21 ± 12	16 ± 7	0.08	26 ± 9	15 ± 8	0.002
Race (white) (%)	90.3	87.1	0.64	85.7	92	0.47	100	81.3	0.13
Waist (cm)	86 ± 9	84 ± 9	0.29	85 ± 10	87 ± 8	0.49	87 ± 8	80 ± 8	0.02
Waist/hip ratio	0.86 ± 0.06	0.82 ± 0.05	0.002	0.86 ± 0.06	0.85 ± 0.04	0.31	0.86 ± 0.06	0.78 ± 0,04	0.001
BMI (kg/m^2)	25 ± 3.5	25 ± 3.4	0.35	24 ± 3.2	26 ± 3.2	0.02	26 ± 3.4*	25 ± 4	0.21
SBP (mmHg)	126 ± 17	120 ± 15	0.08	124 ± 16	122 ± 15	0.70	131 ± 17	117 ± 13	0.01
DBP (mmHg)	77 ± 9	77 ± 11	0.99	76 ± 10	78 ± 12	0.48	78 ± 8	75 ± 9	0.39
Hypertension (%)	58	23	0.001	52	30	0.08	70	12.5	<0.001
Current smokers (%)	12	12	0.9	10	8	0.80	20	16	0.64
Insulin dose/kg (U/kg)	0.69 ± 0.29	0.70 ± 0.20	0.92	0.74 ± 0.30	0.68 ± 0.20	0.43	0.57 ± 0.25	0.72 ± 0.23	0.12
Diabetic retinopathy (%)	65.5	40.6	0.02	55	44	0.42	100*	37	0.001
Diabetic nephropathy (%)	38	20	0.06	27	23.5	0.78	50	12.5	0.01
Metabolic syndrome (%)	32	13	0.02	24	16	0.47	50	9.4	0.004

* P < 0.05 between women and men with CAC+, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 2: Laboratory data of patients with and without CAC

	All Patients			Men			Women		
	CAC +	CAC –		CAC +	CAC –		CAC +	CAC –	
	n = 31	n = 69	P	n = 21	n = 37	P	n = 10	n = 32	P
Total cholesterol (mg/dl)	179 ± 40	177 ± 49	0.87	176 ± 39	166 ± 56	0.46	180 ± 40	189 ± 38	0.51
HDL (mg/dl)	59 ± 21	57 ± 13	0.72	59 ± 21	54 ± 12	0.26	60 ± 21	61 ± 14	0.76
LDL (mg/dl)	100 ± 30	102 ± 44	0.82	99 ± 29	96 ± 53	0.83	101 ± 33	108 ± 28	0.47
Triglycerides (mg/dl)	89 (37 – 212)	68 (30 – 706)	0.07	88 (37-168)	65 (31-175)	0.18	91 (50-212)	69 (30-706)	0.31
A1c (%)	8.2 ± 1.6	8.6 ± 1.9	0.27	8.5 ± 2.0	8.0 ± 1.5	0.15	8.8 ± 1.9	8.3 ± 1.7	0.48
Fibrinogen (mg/dl)	338 (199 – 468)	298 (176 – 510)	0.03	316 (199-434)	281 (176 – 391)	0.08	405 (312-486)	316 (200-411)	0.07
CRP (mg/L)	2.06 (0.16 – 27)	3.13 (0.16 -23.4)	0.97	0.85 (0.16-6.39)	1.95 (0.16-16.7)	0.17	3.13 (1.15-16.1)	3.2 (0.37 – 7.29)	0.27

eGDR ($mg.kg^{-1}.min^{-1}$)	5.7 (3.2 – 10.6)	8.7 (3.4 – 11.2)	<0.001	6.0 (3.2-10)	8.2 (3.4-10)	0.13	5.5 (3.4-8.0)	9.0 (5.6-11.2)	<0.001
GFR (ml/min per $1.73m^2$)	76 ± 29	86 ± 27	0.08	83 ± 30	92 ± 30	0.27	62 ± 19*	80 ± 22	0.02
UAER µg⁄min	9.8 (3.5 – 1251)	8.9 (0.9 – 476)	0.18	9.8 (3.5 – 473)	9.7 (0.9 – 476)	0.73	9.8 (7.2 – 1251)	8.3 (4.1 – 35)	0.06

* $P < 0.05$ between women and men with CAC+, GDR: glucose disposal rate, GFR: glomerular filtration rate, UAER: urinary albumin excretion rate

CAPÌTULO 4

Masked Hypertension, Night-time Blood Pressure and Diabetic Retinopathy in Patients with Type 1 Diabetes

Short running title: Systolic night-time blood pressure and diabetic retinopathy in type 1 diabetes

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Abstract

Objective: To analyze the blood pressure patterns assessed by ambulatory blood pressure monitoring (ABPM), the prevalence of masked hypertension and the possible association of these parameters with microvascular complications in patients with type 1 diabetes.

Research Design and Methods: A cross-sectional study was conducted in 129 normotensive patients at the office with type 1 diabetes without renal replacement therapy or previous renal transplant, attending the Endocrine Division's outpatient clinic at Hospital de Clínicas de Porto Alegre. All patients were assessed regarding the presence of retinopathy (direct and indirect fundoscopy after mydriasis), urinary albumin excretion rate (UAER, immunoturbidimetry), and they underwent ABPM (Spacelabs 90207).

Results: Masked hypertension was observed in 19 patients (14.7%) of out 129 normotensive patients at the office. Patients with masked hypertension had an increased prevalence of DR. Night systolic blood pressure remained associated with DR, each 5mm Hg increase in the night systolic BP, increased the change of DR by 37% (95% CI: 1.07 - 1.75, P = 0.01). There was no difference between the groups in the proportion of patients with increased albuminuria (micro- and macroalbuminuria).

Conclusions: Masked hypertension was found in 14.7% of type 1 diabetes normotensive patients at the office and it was associated with the presence of DR. Night systolic BP rather than nocturnal dipping BP pattern was an important factor associated with DR.

Key words: Type 1 diabetes, masked hypertension, diabetic retinopathy

Hypertension has been estimated to affect 30 to 43% of type 1 diabetic patients and usually reflects the development of diabetic nephropathy (DN) (1), but there is a proportion of patients with hypertension without any renal involvement. Hypertension is an important risk factor for diabetic retinopathy (DR) (2-4), and DN (5), as well as for the development of the macrovascular complications (6). Ambulatory blood pressure monitoring (ABPM) has become an important tool to assess BP patterns during a 24-h period in patients with diabetes. Abnormal BP patterns during the night, even in the normotensive range, in patients with type 1 diabetes were related to altered renal hemodynamic parameters (7), albuminuria and autonomic dysfunction (8). Additionally, BP levels in the upper limit of normal range were already a significant risk factor for the development of DR in a 6-year prospective study of normotensive type 1 diabetic patients (9).

ABPM has also allowed the identification of a sub-group of patients denominated of masked hypertension. These patients have normal BP at the office but are hypertensive during the ABPM. The prevalence of masked hypertension is around 9% in the general population (10), and 30% in the type 2 diabetes normotensive patients at the office (11) but its presence and prevalence in type 1 patients is unknown. Therefore, the aim of this study was to analyze the BP patterns assessed by ABPM, the prevalence of masked hypertension and the possible association of these parameters with microvascular complications in patients with type 1 diabetes.

Research Design and Methods

A cross-sectional study was conducted in 129 patients with type 1 diabetes, attending the Endocrine Division's outpatient clinic at Hospital de Clínicas de Porto Alegre. Type 1 diabetes was defined based on World Health Organization criteria, i.e., age <40 years at onset of diabetes, a previous episode of ketoacidosis or documented ketonuria,

and mandatory use of insulin for survival. Patients with diagnosis of hypertension or with end-stage renal disease [(ESRD), on a dialysis program or with kidney transplant] were excluded. The Ethics Committee of the hospital approved the project, and written informed consent was obtained from all patients.

Patient evaluation

Patients underwent an interview and clinical examination to record demographic and anthropometric data, as previously described (9). Retinopathy was assessed by direct and indirect ophthalmoscopy after mydriasis by the same ophthalmologist, and for the purpose of this study, patients were classified only according to the presence or absence of any degree of DR.

The presence of DN was defined according to urinary albumin excretion rate (UAER), measured in two out three 24-h urine collections. Patients with microalbuminuria (UAER >20 and <200 μg/min) and macroalbuminuria (UAER >200 μg/min) were analyzed as a group with DN.

The mean of two office blood pressure examinations (measured with a mercury sphygmomanometer using the left arm and with the patient in a sitting position, after a 10-min rest, on the same day as the ABPM, and at the morning) was considered for the analyses.

Ambulatory Blood Pressure Monitoring

ABPM was performed by oscillometry (Spacelabs 90207, ser. nos. 207/024751 and 207/038016, with calibration certification), with a 15-min interval in the daytime and 20-min interval in the night-time periods. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up the next morning.

All ABPM were performed on a regular workday and were considered satisfactory if at least 80% of the measures were appropriate. The patients were classified as normotensive (office BP <140/90 mm Hg and daytime BP <135/85 mmHg in ABPM), masked hypertensive (office BP <140/90 mm Hg without antihypertensive drugs and ≥135/85 mmHg the ABPM) and hypertensive (office BP >140/90 mmHg and BP > 135/85 mmHg in the daytime ABPM or previous diagnosis of hypertension and use of anti-hypertensive medications), but for the purpose of this study patients with hypertension were excluded from the analysis. Patients were defined as dippers if night-to-day ratios for systolic ABPM and diastolic ABPM were ≤ 0.90 and non-dippers if night-to-day ratio > 0.90.

Laboratory Measurements

UAER was measured by immunoturbidimetry (Microal; Ames-Bayer, Tarrytown, NY) (intra-and interassay coefficient variation of 4.5 and 11%, respectively). A1c was measured by a high-performance liquid chromatography system (reference range 4-6%; Merck-Hitachi 9100). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica). Creatinine was measured by the Jaffé method and the lipid profile by a colorimetric method.

Estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, was calculated based on a regression equation: eGDR ($mg.kg^{-1}.min^{-1}$) = 24.4 – 12.97 (waist/hip ratio) – 3.39 x (presence or absence of hypertension) – 0.60 x (Hb_{A1c}) (12). Glomerular filtration rate (GFR) was estimated using the formula of the Modification of Diet in Renal Disease Study (13): 186 x [serum creatinine $^{-1.154}$ x age$^{-0.203}$ x (0.742, if female) x (1.210, if of African ethnicity)].

Statistical analysis

Student's t-test or ^{2} tests were used to compare clinical and laboratorial data. Data were expressed as mean ± S.D., except for UAER, triglycerides and eGDR, which were log-transformed and expressed as median and range. Multiple logistic regression analyses were performed having the presence of DR as the dependent variable and as independent variables: A1c, diabetes duration and blood pressure level (office and ABPM in different models). A $P < 0.05$ was considered significant.

Results

Masked hypertension was observed in 19 patients (14.7%) and consequently 110 patients (85.3 %) were considered to have normal BP levels in the office and during the ABPM. The clinical and laboratory profile of type 1 diabetic patients with normotension and masked hypertension were analyzed (Table 1). Patients with masked hypertension (14.7% of out 129 normotensive patients at the office) had a longer duration of diabetes and an increased prevalence of DR. Only 8 patients classified as normotensive were using ACE inhibitors due to the presence of albuminuria. The other clinical and laboratory characteristics were not different between the two groups, including albuminuria (micro- and macroalbuminuria).

Table 2 presents the BP parameters of the two groups. Patients with masked hypertension had higher systolic and diastolic office BP than normotensive patients. All BP parameters evaluated by ABPM were also higher than normotensive patients. There was no difference between the groups in the proportion of patients with absence of nocturnal BP dipping. The correlation between BP parameters (offices or ABPM values) and UAER was not significant taking into account all patients or in each group separately. To analyze if the use of ACE inhibitors might have interfered on the results, a separate analyses was

performed not including these patients (n=8). There was no change in the BP parameters and the differences between the two groups remained as previously described.

To analyze the BP parameters and the presence of DR, the patients were grouped according the presence or absence of DR. It was observed that patients with DR tended to have higher BP levels at ABPM during the day than patients without DR, but the levels were particularly increased at night, including absence of systolic night-time dipping pattern (Table 3), the only clinical characteristic that was higher in patients with DR was duration of diabetes. To evaluate if BP parameters were independently associated with DR, models of multiple logistic regression analysis were performed with DR as the dependent variable and duration of diabetes, A_{1c} values, and BP levels as independent variables. Different models were constructed with each systolic or diastolic BP value of the office and ABPM, stratified by 5 mm Hg or nocturnal dipping BP. Only night systolic BP (OR: 1.37, 95% CI: 1.07 - 1.75, P = 0.01) and diabetes duration (OR: 1.10 95% CI: 1.03- 1.17, P = 0.002) remained significantly associated with DR.

Conclusions

In this sample of office normotensive patients with type 1 diabetes it was observed that 14.7% had masked hypertension and these patients had a higher proportion of DR. Moreover, an association between night systolic BP and DR was also described. These data reinforced the role of increased BP levels, even in the range considered normal at the office, as an important risk factor for the development of DR.

As far as we know the prevalence of masked hypertension has not yet been described in adult patients with type 1 diabetes. In a recent study in children with type 1 diabetes (5-18 years old), the prevalence of abnormal BP as compared to a control group

was around 5% during the day and 15% at nighttime (14). However office BP values were not presented, so it was not possible to estimate the prevalence of masked hypertension. In type 2 diabetes normotensive patients, the prevalence of masked hypertension is about 30% and it was associated with higher UAER and an enlarged left ventricular wall compared to normotensives (11). However, patients with type 1 diabetes and masked hypertension described in the present study did not have an increased prevalence of micro- or macroalbuminuria, but DR was more frequent.

Analyzing the possible factors associated with DR in this sample of office normotensive type 1 patients with diabetes, increased blood pressure levels particularly at night time emerged as an important factor. Absence of systolic nocturnal dipping was associated with DR only in the univariate analysis, reinforcing the hypothesis that the most important factor to damage the retinal vessels is the night-time value of BP rather than nocturnal dipping pattern. We have previously described, in a 6-year prospective study of a smaller sample of office normotensive and normoalbuminuric patients with type 1 patients, that high normal ABPM levels were the main risk factor for the development of DR (9). Other authors have also suggested the night-time BP were associated with the presence and severity of DR in a cross-sectional study with normotensive type 1 patients with diabetes (15). Recently, BP means rather than nocturnal dipping pattern were associated with diabetic complications, including DR (16). Autonomic neuropathy has also been associated with DR development (17), and poor auto regulation of retinal blood vessels might result in increased retinal blood flow and render the retinal arteriolar and capillary beds more susceptible to damage by increased BP levels (18). The association of night-time BP levels with DR in the present study might be due to higher levels of BP in the supine position due to some degree of autonomic dysfunction. Although autonomic neuropathy was not

evaluated in the present study we can speculate that these increased BP levels would have a greater impact on retina blood vessel with impaired autoregulation.

The possible limitations of this study are the cross-sectional design that does not allow for a causal relationship and fundus photographs were not done. However, this probably did not compromise the main results of the study since we and others have previously observed a high agreement between direct and indirect ophthalmoscopy after mydriasis (19, 20). Moreover, absence of stereoscopic photography might at most underestimate the prevalence of DR.

Prospective studies of the treatment of patients with masked hypertension will be important to define the best strategy to deal with this situation.

In conclusion, masked hypertension was found in 14.7% of normotensive patients with type 1 diabetes and it was associated with the presence of DR. Moreover, night systolic BP was an important factor associated with DR. ABPM should be used as an additional tool in the periodical assessment of type 1 diabetic patients, especially those with normal BP at the office.

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Table 1: Clinical and Laboratory data according to the blood pressure profile

	Normotension (n=110)	**Masked Hypertension (n=19)**	**P**
Men n (%)	59 (53.6)	10 (52.6)	0.93
Age (years)	32 ± 10	35 ± 8	0.22
Diabetes duration (years)	14 ± 7	18 ± 8	0.04
Ethnicity (white) n (%)	98 (89)	18 (95)	0.72
Current smoking (%)	11 (10.5)	4 (23.5)	0.17
Waist circumference (cm)			
Men	83 ± 8	88 ± 13	0.09
Women	79 ± 7	85 ± 10	0.06
BMI (kg/m^2)	24 ± 3	25 ± 3	0.17
Insulin dose/kg (U/kg)	0.74 ± 0.27	0.77 ± 0.15	0.54
A1c (%)	8.2 ± 1.8	8.3 ± 2.0	0.93
Total cholesterol (mg/dl)	175 ± 43	172 ± 32	0.77
HDL cholesterol (mg/dl)	57 ± 13	59 ± 20	0.74
LDL cholesterol (mg/dl)	101 ± 38	97 ± 35	0.72
Triglycerides (mg/dl)	67 (22 – 256)	61 (32 – 163)	0.24
eGDR ($mg.kg^{-1}.min^{-1}$)	9.0 (3.0 -11.6)	8.1 (5.7-10.5)	0.24
GFR (ml/min per $1.73m^2$)	92 ± 27	87 ± 19	0.49
Diabetic nephropathy n (%)	19 (17)	4 (17.6)	0.89
Diabetic retinopathy n (%)	36 (33.3)	11 (58)	0.04

Data are means ± SD, median (range) or %.

Table 2: Blood pressure parameters in patients with type 1 diabetes with normotension and masked hypertension.

	Normotension (n=110)	**Masked Hypertension (n=19)**	**P**
Office BP (mmHg)			
Systolic	114 ± 11	124 ± 8	<0.001
Diastolic	74 ± 9	79 ± 7	0.006
Ambulatory BP (mmHg)			
24-h systolic	116 ± 8	130 ± 5	<0.001
24-h diastolic	71 ± 7	82 ± 5	<0.001
Day systolic	118 ± 8	133 ± 5	<0.001
Day diastolic	74 ± 6	86 ± 5	<0.001
Night systolic	110 ± 11	120 ± 8	<0.001
Night diastolic	64 ± 7	72 ± 7	<0.001
Night-time/Daytime ratio			
Systolic	0.89 ± 0.04	0.90 ± 0.05	0.14
Diastolic	0.86 ± 0.08	0.83 ± 0.07	0.15
Absence of nocturnal BP dipping n (%)			
Systolic	70 (64)	9 (47)	0.16
Diastolic	38 (35)	4 (21)	0.23

Values are mean ± SD and %.

Table 3: Blood pressure parameters in patients with type 1 diabetes without retinopathy and with retinopathy

	Without Retinopathy (n = 82)	**With Retinopathy (n = 47)**	**P**
Diabetes duration (years)	13 ± 6	18 ± 6	<0.001
Office BP (mmHg)			
Systolic	114 ± 11	118 ± 11	0.11
Diastolic	74 ± 9	76 ± 8	0.31
Ambulatory BP (mmHg)			
24-h systolic	117 ± 8	120 ± 9	0.05
24-h diastolic	72 ± 8	75 ± 7	0.08
Day systolic	120 ± 9	122 ± 8	0.15
Day diastolic	75 ± 7	78 ± 7	0.03

Night systolic	109 ± 10	115 ± 11	0.003
Night diastolic	64 ± 6	68 ± 8	0.004
Night-time/Daytime ratio			
Systolic	0.91 ± 0.06	0.94 ± 0.05	0.008
Diastolic	0.85 ± 0.08	0.87 ± 0.08	0.17
Absence of nocturnal BP dipping n (%)			
Systolic	44 (54)	34 (72)	0.04
Diastolic	24 (29.5)	17 (36)	0.43

Values are mean ± SD and %.

References:

1- Arauz-Pacheco C, Parrot MA, Raskin P: The treatment of hypertension in adult patients with diabetes. *Diabetes Care* 25: 134-147, 2002

2- Klein R, Klein BEK, Moss BE, Davis MD, DeMets DL: Is blood pressure a predictor of the incidence or progression of diabetic retinopathy. *Arch Intern Med* 149: 2427-2432, 1989

3- Janka HU, Warram JH, Rand LI, Krolewski AS: Risk factors for progression of background retinopathy in long-standing IDDM. *Diabetes* 38: 460-464, 1989

4- Sjolie AK, Stephenson J, Aldington S, Kohner E, Janka H, Stevens L, Fuller J: Retinopathy and vision loss in insulin dependent diabetes in Europe: the EURODIAB IDDM Complications Study. *Ophthalmology* 104: 252-260, 1997

5- Mogensen CE: Progression of nephropathy in long-term diabetics with proteinuria and the effect of initial anti-hypertensive treatment. *Scand Clin Lab Invest* 36: 383-388, 1976

6- Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ: Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis* 148: 159-169, 2000

7- Pecis M, Azevedo MJ, Gross JL. Glomerular hyperfiltration is associated with blood pressure abnormalities in normotensive normoalbuminuric IDDM patients. *Diabetes Care* 20:1329-1333, 1997

8- Pecis M, Azevedo MJ, Moraes RS, Ferlin EL, Gross JL. Autonomic dysfunction and urinary albumin excretion rate are associated with an abnormal blood pressure pattern in normotensive normoalbuminuric type 1 diabetic patients. *Diabetes Care* 23: 989-993, 2000

9- Rodrigues TC, Pecis M, Azevedo MJ, Esteves JF, Gross JL: Ambulatory Blood Pressure Monitoring and Progression of retinopathy in normotensive, normoalbuminuric type 1 diabetic patients: A 6 - year follow-up study. *Diabetes Res Clin Pract* 74: 135-140, 2006

10- Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Malion J-M : Cardiovascular prognosis of masked hypertension detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 291: 1342- 1350, 2004

11- Leitão CB, Canani LH, Kramer CK, Boza JC, Pinotti AF, Gross JL: Masked Hypertension, Urinary Albumin Excretion Rate, and Echocardiographic Parameters in Putatively Normotensive Type 2 Diabetic Patients. *Diabetes Care* 30: 1255-1260, 2007

12- Williams KV, Erbey JR, Becker D, Arsianian S, Orchard TJ: Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 49: 626-632, 2000

13- Levey AS, Coresh J, balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G: National Kidney Foundation practice guidelines for chronic kidney: evaluation, classification, and stratification. *Ann Intern Med* 139: 137-147, 2003

14- Dost A, Klinkert C, Kapellen T, Lemmer A, Naeke A, Grabert M, Kreuder J, Holl RW. Arterial Hypertension Determined By Ambulatory Blood Pressure Profiles: Contribution to Microalbuminuria Risk In A Multicenter Investigation In 2105 Children And Adolescents With Diabetes Mellitus Type 1. *Diabetes Care* 31: 720-725, 2008

15- Klein R, Moss SE, Simaiko AR, Zinman B, Gardiner R, Suissa S, Donnelly SM, Kramer MS, Goodyer P, Strand T, Mauer M: The Relation of Ambulatory Blood Pressure and Pulse Rate to Retinopathy in Type 1 Diabetes Mellitus. *Ophthamology* 113: 2231-2236, 2006

16- Leitão CB, Canani LH, Kramer CK, Moehlecke M, Pinto LC, Ricardo ED, Pinotti AF, Gross JL. Blood pressure means rather nocturnal dipping pattern are related to complications in type 2 diabetic patients. *Diabet Med* 25: 308-313, 2008

17- Krolewski AS, Barzilay J, Warram JH, Martin BC, Pfeifer M, Rand LI: Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy. *Diabetes* 41: 430-437, 1992

18- Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. *Diabetes* 44: 603-607, 1995

19- Boelter MC, Gross JL, Canani LH, Costa LA, Lisboa HR, Três GS, Lavinsky J, Azevedo MJ. Proliferative diabetic retinopathy is associated with microalbuminuria in patients with type 2 diabetes. *Braz J Med Biol Res* 39: 1033-1039, 2006

20- Hutchinson A, McIntosh A, Peters J, O´Keeffe C, Khunti K, Baker R, Booth A. Effectiveness of screening and monitoring tests for diabetic retinopathy. *Diabet Med* 17: 495-506, 2000

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