UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

DISSERTAÇÃO DE MESTRADO

ANORMALIDADES DA HOMEOSTASE PRESSÓRICA IDENTIFICADAS ATRAVÉS DA MONITORIZAÇÃO AMBULATORIAL DA PRESSÃO ARTERIAL:

ESTUDO TRANSVERSAL EM ADULTOS COM DIFERENTES GRAUS DE TOLERÂNCIA À GLICOSE

VANESSA PICCOLI

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VANESSA PICCOLI

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Dissertação de mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul como requisito para obtenção do título de Mestre.

Porto Alegre, 2016

DEDICATÓRIA

Aos pacientes.

"To study the phenomenon of disease without books is to sail an uncharted sea,

while to study books without patients is not to go to sea at all."

Sir William Osler

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LISTA DE ABREVIATURAS – Português:

A1c - Hemoglobina glicada

ACTH – Hormônio adrenocorticotrófico

DM - Diabetes mellitus

GJA - Glicemia de jejum alterada

HAS - Hipertensão arterial sistêmica

IMC - Índice de massa corporal

MAPA - Monitorização ambulatorial da pressão arterial

PA - Pressão arterial

PDM - Pré-diabetes

PP – Pressão de pulso

TDG - Tolerância diminuída à glicose

TOTG - Teste oral de tolerância à glicose

A1c – Glycated hemoglobin

ABPM – Ambulatory blood pressure monitoring

ACTH – Adrenocorticotropic hormone

AIDS – Acquired Immune Deficiency Syndrome

BMI – Body mass index

BP – Blood pressure

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration) equation

DBP - Diastolic blood pressure

eGFR – Estimated glomerular filtration rate

FPG – Fasting plasma glucose

GEE – Generalized estimating equation

GT – Glucose tolerance

HOMA-IR – Homeostatic model assessment-insulin resistance

IFG – Impaired fasting glucose

IGM – Impaired glucose metabolism

IGT – Impaired glucose tolerance

ISI – Insulinn sensitivity index

NGT – Normal glucose tolerance

NHANES – National Health and Nutrition Examination Survey

OGTT – Oral glucose tolerance test

PDM - Prediabetes

PP – Pulse pressure

SBP – Systolic blood pressure

SD – Standard deviation

STROBE – Strengthening the Reporting of Observational studies in Epidemiology

T2DM – Type 2 diabetes mellitus

UAE – Urinary albumin excretion

US-CRP – Ultra sensitive C-reactive protein

WC – Waist circumference

I – INTRODUÇÃO

Diabetes Mellitus, Pré-Diabetes e Pressão Arterial

Resumo:

O pré-diabetes (PDM), da mesma forma que o diabetes mellitus (DM), associa-se com complicações micro e macrovasculares. Existem evidências de que existem anormalidades da homestoase da pressão arterial em indivíduos com PDM.

Através da monitorização ambulatorial da pressão arterial (MAPA) é possível identificar o padrão de homeostase pressórica de indivíduos com diferentes graus de tolerância à glicose. Evidências demonstram que as medidas de pressão arterial (PA) obtidas por MAPA apresentam melhor associação com lesões de órgãos alvo se comparadas a medidas obtidas em consultório. Medidas de PA obtidas através de MAPA demonstram melhor correlação com complicações crônicas microvasculares do DM. Entretanto, dispõe-se de poucos dados na literatura sobre o comportamento da pressão arterial de 24 horas em indivíduos com PDM.

Este trabalho é inicialmente constituído de uma revisão direcionada sobre homeostase pressórica em indivíduos com diferentes graus de tolerância à glicose seguido de um artigo original a respeito do tema. O artigo se trata de um estudo transversal que avaliou o padrão de homeostase pressórica de 24 horas em 138 indivíduos com diferentes graus de tolerância à glicose. O estudo demonstrou que através da MAPA é possível observar uma elevação dos níveis de pressão arterial ao longo de 24 horas de acordo com a piora da tolerância à glicose.

Descritores: pressão arterial, monitorização ambulatorial da pressão arterial, *diabetes mellitus,* pré-diabetes

Abstract:

As diabetes mellitus (DM), prediabetes is associated with microvascular and macrovascular complications. There is evidence of presence of abnormalities in blood pressure (BP) homeostasis in individuals with prediabetes (PDM).

Ambulatory blood pressure monitoring (ABPM) enables to identify the pattern of BP homeostasis in individuals with different degrees of glucose tolerance. Evidences have shown that BP measurements obtained by ABPM have a better association with target organ damage compared to measurements obtained in the office. Studies have also shown better correlation of BP measurements obtained by ABPM with microvascular chronic complications of DM. However, there are few data in literature about the behavior of 24 hours BP in subjects with prediabetes.

This study consists of a review focused on BP homeostasis in subjects with different degrees of glucose tolerance and an original article about this issue. This is a cross-sectional study that evaluated how BP homeostasis behaves along 24 hours in 138 subjects with different degrees of glucose tolerance. The study demonstrated that through the ABPM is possible to observe an increase in blood pressure levels over 24 hours according to a worsening of glucose tolerance.

Key words: blood pressure, ambulatory blood pressure monitoring, diabetes, prediabetes

1. Introdução

Diabetes mellitus (DM) tipo 2 e hipertensão arterial sistêmica (HAS) são doenças crônicas altamente prevalentes e comumente associadas. Aproximadamente dois terços dos pacientes com DM tipo 2 apresentam HAS.[1-3]

Ao longo do último século houve uma transição do perfil de morbimortalidade na população brasileira. As doenças infecto-parasitárias, que por volta de 1930 causavam cerca de 46% das mortes na população das capitais, passaram a representar apenas 10%. Com o aumento da expectativa de vida e melhor controle das doenças infecto-parasitárias houve um aumento na mortalidade por doenças crônico-degenerativas. Assim como em todo o mundo, no Brasil as doenças cardiovasculares destacam-se entre as principais causas de morbidade e mortalidade, sendo que, de forma independente ou associada, o DM e a HAS aparecem entre os principais fatores de risco.[4,5]

O setor público dispende anualmente elevados gastos decorrentes do tratamento das complicações de doenças crônicas. No Brasil, em 2007, o DM foi responsável direto por 123.483 internações, gerando um gasto público de R$ 52.409.158,30. No ano de 2005, no estado de São Paulo, 32,3% dos óbitos foram decorrentes de doenças cardiovasculares; sendo que, em 2007, estas geraram 263.284 internações a um custo de R$ 405.387.635,94.[5]

Não apenas indivíduos com DM, mas também indivíduos com pré-diabetes (PDM), definidos pela presença de glicemia de jejum alterada (GJA) e/ou tolerância diminuída à glicose (TDG), demonstram ter maior prevalência de HAS, se comprados à população sem anormalidades do metabolismo da glicose.[6-8] Este achado deve-se, em parte, à elevada prevalência de sobrepeso e obesidade, tanto em populações de países desenvolvidos como de países em desenvolvimento.[9-12] Entretanto, apenas o excesso de peso não parece justificar a associação entre anormalidades do metabolismo da glicose e a HAS.[1,13]

A obesidade acarreta uma série de anormalidades metabólicas que levam ao DM e a HAS.[14-16] Portanto, torna-se útil o conhecimento aprofundado das anormalidades dos padrões metabólicos e da homeostase pressórica não apenas no final do espectro dessas anormalidades, quando se realiza o diagnóstico de DM, mas das alterações metabólicas que as precedem, como as que ocorrem no PDM.[17-20] Identificar e compreender os possíveis determinantes e os padrões de alteração da homeostase pressórica em estágios

precoces de alteração do metabolismo da glicose é útil para que se possa definir abordagens de prevenção primária que visem contribuir para uma melhor qualidade de vida dos indivíduos e que levem a menores índices de morbidade e de mortalidade por complicações decorrentes do DM associado à HAS.

DM e anormalidades da homeostase pressórica apresentam um elo em comum e de provável relação de causa e efeito não completamente definido.[1,3,21] A associação entre hiperglicemia sustentada e HAS é fator de risco para o aparecimento e progressão das complicações micro e macrovasculares do DM, sendo estas também já demonstradas em indivíduos com PDM.[22-25] Reconhecer precocemente as alterações do metabolismo da glicose e da pressão arterial (PA) é fundamental na prevenção das complicações vasculares do DM, responsáveis por elevadas taxas de morbidade e mortalidade.[26-28]

2. Epidemiologia

A prevalência estimada de HAS em países subdesenvolvidos e desenvolvidos é de 37,3% e 22,9%, respectivamente.[29] Existe uma projeção de aumento de 60% na prevalência de indivíduos hipertensos para o ano de 2025.[29] Em estudo de meta-análise, Picon et al. avaliaram 40 estudos transversais e de coorte, incluindo 122.018 indivíduos, demonstrando que a prevalência estimada de HAS na população brasileira é de cerca de 30%.[30]

A prevalência de DM na população americana avaliada pelo *National Health and Nutrition Examination Survey* (NHANES) entre 1999 e 2002 é de 6,5%, sendo semelhante entre ambos os sexos e chegando a 15,8% em indivíduos com idade acima de 65 anos.[31] Na região sul do Brasil, a prevalência de DM e de TDG em adultos acimda de 30 anos foi de respectivamente 7,6% e 7,8% em 1992.[32]

Segundo o NHANES, entre 2005 e 2008, a prevalência de PDM na população americana, definida por glicemia de jejum e hemoglobina glicada (A1c), foi de 35% na população acima de 20 anos e de 50% na população acima de 65 anos.[33] Aproximadamente 5 a 10% de indivíduos com PDM progride para DM anualmente, sendo que esta taxa varia de acordo com as características de cada população e com os critérios utilizados para definir PDM. A prevalência de HAS em indivíduos com PDM

foi de 56%, sendo de 58% em indivíduos com GJA, 55% em indivíduos com TDG e 60% em indivíduos que apresentam GJA e TDG no estudo NHANES III.[27,34]

O estudo "*Relationship between Insulin Sensitivity and Cardiovascular Disease*" (RISC), uma coorte multicêntrica europeia, que incluiu 1.308 indivíduos saudáveis, sem histórico de HAS e de DM, estudou fatores relacionados ao desenvolvimento da HAS. O estudo submeteu os indivíduos a bioimpedanciometria elétrica, teste oral de tolerância à glicose (TOTG) e clamp euglicêmico hiperinsulinêmico e avaliou o impacto da obesidade, distribuição de gordura abdominal, resistência à insulina e resposta à insulina no desenvolvimento de HAS. Idade, história familiar de HAS, menopausa, índice de massa corporal (IMC), circunferência abdominal, tabagismo, DM ou TDG demonstraram ser fatores de risco independentes associados ao aumento dos níveis de pressão arterial sistêmica medidos no consultório.[35]

3. Patogênese

O desenvolvimento de HAS em pacientes com DM tem relação bem estabelecida com o desenvolvimento de albuminúria. Entretanto, indivíduos sem evidências de nefropatia diabética são suscetíveis ao desenvolvimento de anormalidades da homeostase pressórica. Além de lesão renal, outros fatores são propostos como desencadeantes de HAS em indivíduos com DM, ambos relacionados à hiperinsulinemia e resistência à insulina: aumento da absorção de sódio no túbulo contorcido proximal, expansão do volume intravascular e aumento da resistência vascular.[1,2,21,36] Receptores de insulina estão presentes ao longo de todo o tecido renal e sua ação contribui para reabsorção de sódio no túbulo contorcido proximal, alça ascendente, túbulo distal e ducto coletor. Portanto em indivíduos com alteração do metabolismo da glicose, o estado de hiperglicemia contribui para exacerbação suprafisológica da reabsorção de sódio, contribuindo para a expansão do volume intravascular.[36]

A HAS é caracterizada pelo aumento da resistência vascular periférica e por disfunção endotelial, enquanto que o DM caracteriza-se por resistência à insulina e disfunção de células β pancreáticas. A fisiopatologia destas duas doenças apresenta um vínculo em comum, sendo que a obesidade é o mais importante fator de risco para o desenvolvimento de ambas e também fator confundidor na relação entre glicemia e pressão arterial.[14,35]

A resistência à insulina é um elo bem estabelecido entre obesidade, TDG, DM e HAS.[1,21] O exato mecanismo pelo qual as anormalidade na ação da insulina em seus tecidos alvos contribuem para elevação nos níveis de pressão arterial são ainda não completamente esclarecidos. Resistência à insulina leva à menor vasodilatação por mecanismo de disfunção endotelial, presente em indivíduos com HAS ou DM. Associada à resistência à insulina, através de mecanismo de *feedback* por diminuição da resposta intracelular, a hiperinsulinemia também contribui para o desenvolvimento de HAS em indivíduos com alterações do metabolismo da glicose.[1,2,21]

4. Monitorização ambulatorial da pressão arterial

A monitorização ambulatorial da pressão arterial (MAPA) fornece dados referentes à média da PA de 24 horas, média de PA diurna (período de vigília), PA noturna (período de sono), carga pressórica sistólica e diastólica, e descenso noturno da PA.

A MAPA de 24 horas fornece informações impossíveis de obter através de medidas únicas em consultório. Tais dados, se comparados a medidas isoladas de PA em consultório, demonstram contribuir para melhor estratificação de risco cardiovascular não apenas na população em geral, como também em indivíduos com DM e HAS.[37,38] A avaliação dos níveis de PA através de MAPA demonstra melhor associação com lesão em órgãos alvo, quando comparado a medidas de PA em consultório.[37,38]

Adicionalmente, as medidas de PA obtidas através de MAPA de 24 horas demonstram contribuir para melhor estratificação de risco cardiovascular, predição de mortalidade e de eventos cardiovasculares, se comparadas a medidas de PA em consultório, tanto na população em geral como em indivíduos hipertensos.[37,39]

Uma série de estudos tem demonstrado que indivíduos com DM e HAS apresentam a medida da pressão arterial pela MAPA no dia e na noite maior que os pacientes que apresentam apenas hipertensão essencial, sugerindo que os mecanismos de desenvolvimento para a hiperglicemia estejam direta ou indiretamente relacionados ao desenvolvimento da HAS no DM, mesmo quando ajustados para outros determinantes da homeostase pressórica e desenvolvimento de HAS.[8,40,41]

Estudos também demonstram melhor correlação de medidas de PA através de MAPA, como média de PA de 24h, pressão do período de vigília e de sono, com complicações crônicas do DM e predição de seu desenvolvimento, destacando-se as complicações renais, além de mortalidade cardiovascular e geral.[38,42,43]

Ao se estudar o ritmo circadiano da homeostase da pressão arterial é observado em indivíduos sadios uma queda dos níveis de PA durante o sono, sendo que se considera dentro da normalidade uma queda maior do que 10% dos níveis de PA noturna em relação à PA diurna. A ausência do descenso noturno é caracterizada por uma queda <10% da PA noturna em relação à PA diurna e define os indivíduos como *non-dippers*.[41] Indivíduos *non-dippers* com ou sem DM tendem a apresentar taxas mais elevadas de lesão de órgãos alvo, maior incidência de eventos cardiovasculares fatais e não fatais.[40] Entretanto, estudos prospectivos ainda não demonstram relação definitiva quanto a esta informação.

Chen et al., com o objetivo de avaliar possíveis causas de TDG em indivíduos com HAS, submeteu 50 pacientes hipertensos e com índice de massa corporal (IMC) <30 kg/m^2 (n=25 *dippers*, n=25 *non-dippers*) a TOTG, avaliação da atividade do sistema nervoso autônomo (análise espectral) e dosagens hormonais sérica (catecolaminas, T4, aldosterona, renina, hormônio do crescimento) e urinária de 24 horas (cortisol, catecolaminas, dopamina). O estudo demonstrou que os indivíduos *non-dippers* apresentam maior frequência de TDG do que os *dippers*. Os indivíduos *non-dippers* demonstraram ter maior ativação do tônus simpático, atividade parassimpática diminuída e níveis mais elevados de catecolaminas séricas, sugerindo que uma maior ativação do sistema nervoso simpático e uma menor ativação do parassimpático resultam e uma disfunção autonômica que contribui para um aumento da PA e serve como um elo na associação entre HAS e alterações do metabolismo da glicose.[44]

Cardoso et al. avaliou a associação entre a PA obtida em consultório e a PA obtida através de MAPA de 24 horas e a presença de complicações microvasculares (retinopatia, presença de microalbuminúria, nefropatia e neuropatia) e macrovasculares (doença coronariana, doença cerebrovascular e doença arterial periférica) do DM. Este estudo, que avaliou 550 pacientes com DM tipo 2, demonstrou que as medidas de PA obtidas através de MAPA apresentam melhor correlação com complicações micro e macrovasculares do DM do que medidas de PA em consultório, sendo as medidas de PA noturna preditoras mais importantes do que as medidas diurnas.[38] Salles et al. avaliou este

mesmo grupo de pacientes, em estudo de coorte prospectiva, e investigou o impacto prognóstico de medidas de PA obtidas em consultório e através de MAPA quanto à morbidade e mortalidade em indivíduos com DM tipo 2. Os paciente foram acompanhados durante uma média de 5,7 anos. O estudo demonstrou que a MAPA fornece dados mais consistentes para a estratificação de risco cardiovascular, se comparado à medidas de PA em consultório. Adicionalmente, neste estudo, níveis de PA de 24 horas inferiores a 120/75mmHg apresentaram associação com significativa proteção cardiovascular.[45]

Os limites de normalidade e para hipertensão de acordo com a MAPA são:

- PA média de 24h: PA normal é definida como menor do que 125/75 mmHg e hipertensão é definida como ≥ 130/80 mmHg

- PA média diurna: PA normal é definida como < 130/85 mmHg e hipertensão é definida como ≥ 140/85 mmHg

- PA média noturna: PA normal é definida como < 110/70 mmHg e hipertensão é definida como ≥ 120/70 mmHg. [46]

Durante 24 horas a pressão arterial caracteriza-se por apresentar variabilidade ao longo deste período, com níveis menores durante a manhã, que se elevam progressivamente ao longo do dia, com um vale no período pós prandial e descenso progressivo dos níveis ao longo da noite até o início da manhã.[47,48]

A maioria dos estudos disponíveis sobre avaliação dos diferentes padrões de pressão arterial avalia apenas grupos específicos tais como indivíduos saudáveis ou com presença de hipertensão essencial ou com DM. São escassos os dados sobre comparações do perfil de PA ao longo de 24 horas entre grupos de indivíduos sem comorbidades e indivíduos com alterações do metabolismo da glicose.[40,41,49]

5. Pré-diabetes e Monitorização Ambulatorial da Pressão Arterial

O PDM, assim como o DM, é associado a complicações micro e macrovasculares.[24,25,50] Existem evidências de que a homeostase da PA em indivíduos com PDM é anormal.[21,27,48,51,52]

Pequenos estudos tem sugerido que a pressão média de 24 horas sistólica e diastólica é maior em indivíduos com PDM se comparados a indivíduos normais.[20,48]

Putz et al. comparou 75 indivíduos com TDG com 40 indivíduos voluntários saudáveis submetidos a avaliação da pressão arterial através de MAPA de 24 horas. No estudo demonstrou-se que os níveis de pressão arterial sistólica e diastólica de 24 horas, do período de vigília e de sono, mesmo após ajuste para IMC, foram maiores nos indivíduos com TDG.[20]

Gupta et al. avaliou anormalidades da homeostase pressórica através da realização de MAPA durante 7 dias consecutivos em 12 indivíduos obesos em fase de triagem para estudo de intervenção para perda de peso. Os indivíduos com PDM (n=6; GJA e/ou TDG) demonstraram níveis mais elevados de pressão arterial do que os indivíduos normoglicêmicos, mesmo após ajuste para sexo, idade, raça, IMC e circunferência abdominal.[48]

Estudos experimentais também demonstram associação entre alterações do metabolismo da glicose e alterações da homeostase pressórica. Ratos submetidos a dietas de baixo índice glicêmico e baixo teor de gorduras (n=9; dieta padrão; DP) vs. alto índice glicêmico e alto teor de gorduras (n=10; dieta Americana; DA), durante 6 meses, demonstraram diferentes níveis de pressão arterial. Os ratos alimentados com DA desenvolveram níveis mais elevados de marcadores inflamatórios, aumento de peso, resistência à ação da insulina, aumento da glicemia de jejum assim como níveis mais elevados de pressão arterial sistólica e diastólica ao longo de 24 horas do que os submetidos à DP. Ao fim do estudo, realizou-se pesagem de órgãos (rins e coração) dos animais e observou-se que os ratos submetidos à DA apresentavam órgãos mais pesados e com maior deposição externa de gordura.[51]

Os estudos apresentandos sugerem que ocorre um aumento dos níveis de PA com a piora da tolerância à glicose (TG). Entretanto, pouco se sabe sobre quais fatores estão envolvidos neste processo e como a PA se comporta ao longo do dia em indivíduos com diferentes graus de TG, principalmente nos estágios mais precoces de alteração do metabolismo da glicose.[21]

Conclusões

O uso de MAPA na rotina da avaliação clínica de indivíduos com alterações do metabolismo da glicose pode contribuir para a identificação precoce de anormalidades da homeostase pressórica, as quais correlacionam-se com maior risco para o desenvolvimento de complicações micro e macrovasculares.

O dados na literatura sobre anormalidades da homeostase pressórica em indivíduos com PDM são escassos, assim como dados sobre pontos de corte de pressão arterial obtidos através de MAPA que se correlacionem com complicações micro e macrovasculares.

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II - OBJETIVOS

- Investigar como a pressão arterial, obtida através de monitorização ambulatorial da pressão de 24 horas, comporta-se em indivíduos com diferentes graus de tolerância à glicose.

- Estudar fatores relacionados ao comportamento da pressão arterial.

III – ARTIGO ORIGINAL EM INGLÊS

Ambulatory blood pressure monitoring in subjects with different degrees of glucose tolerance: a cross-sectional study in adults

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ABSTRACT

Summary: It is poorly understood how circadian blood pressure (BP) behave among subjects with impaired glucose metabolism.

Aim: To investigate how BP, obtained by 24-h blood pressure monitoring (ABPM), behaves in subjects with different degrees of glucose tolerance (GT) and to study factors related to BP behavior.

Methods: Cross-sectional study of 138 consecutive adult patients referred for ambulatory care, whose glycemic status was not previously defined. Patients were submitted to clinical and anthropometrical evaluation. Blood and 24-h urine samples were collected. 75g oral glucose tolerance test (OGTT) was performed. BP levels were obtained by office and 24-h ABPM measurements. Antihypertensive treatment scheme was stopped one week before data collection.

Results: Subjects were divided by glucose tolerance in normal glucose tolerance (NGT; n = 39), impaired glucose metabolism (IGM: n = 55) and diabetes (DM; n = 44). These three groups did not differ by gender distribution, years of schooling, smoking status, estimated glomerular filtration rate (eGFR), insulin, cortisol, adrenocorticotropic hormone (ACTH) levels, and the 24-h urinary levels of normetanephrines and metanephrines. Age, BMI, WC, plasma glucose, plasma cortisol and 24-h UAE were positively related to 24-h systolic blood pressure (SBP), whereas years of schooling, ISI Stumvoll, eGFR were inversely related to it. By ABPM, 24-h, daytime and nighttime SBP levels progressively increased from NGT to DM. Diastolic blood pressure levels had the same pattern by daytime, nighttime and 24-h, however these differences did not reach statistical significance. Pulse pressure (PP) increased from NGT to DM. Multiple linear regression models were performed and glucose tolerance showed to be the most

important determinant of 24-h SBP, even after adjustments for gender, age, WC, 24-h UAE, years of schooling and serum cortisol.

Conclusions: This study provides evidence that SBP and PP levels increase with decreasing of GT, independently of age, sex, education, UAE and cortisol levels.

Key words: glucose tolerance, prediabetes, diabetes, blood pressure, ambulatory blood pressure monitoring

INTRODUCTION

Prediabetes (PDM) is highly prevalent in adults and it has been linked to micro- and macrovascular complications only related, in the past, to type 2 diabetes mellitus (T2DM).[1-5] Although the risk of developing these complications is lower in subjects with PDM than those with T2DM, the prevalence of PDM is much higher and, as a consequence, the population attributable risk of developing those vascular complications may be similar in both states of abnormal glucose metabolism.[6,7] Since arterial hypertension is highly prevalent in subjects with T2DM and is considered a major contributor to its related vascular complications, is important to understand how blood pressure homeostasis behaves in subjects with PDM and to identify factors related to abnormalities of its homeostasis in subjects with PDM. [8-12]

Several factors have been related to the development of arterial hypertension in T2DM and may be related to its development in PDM. Insulin resistance and its resulting hyperinsulinemia, a key feature of T2DM, may enhance salt absorption in the proximal tubule, causing a state of salt overload, volume expansion, and arterial hypertension. Hyperinsulinemia also activates the sympathetic nervous system, increases calcium concentration in smooth muscle cells, worsening vascular resistance and increasing arterial blood pressure. [12-14]

Additionally, visceral fat accumulation, chronic inflammation and increased urinary albumin excretion (UAE) are common features of subjects who develop T2DM and arterial hypertension and may be related to abnormalities of blood pressure (BP) homeostasis in subjects with PDM. [15-19]

Data regarding how BP behaves in subjects with PDM is limited and mostly performed by its office measurements. Abnormalities of BP homeostasis have been identify in small studies of subjects with PDM.[20-22]

It is well known that BP exhibits variation along the 24 hours of the day. However, in clinical practice, BP measurements are usually obtained in the office, providing limited and discrepant information.[23] For this reason, ABPM has been increasingly recommended due to its accurate readings and blood pressure assessment outside the artificial behavior of the clinic. [24,25]

The objective of this study was to understand how BP behaves in subjects with PDM, compared to subjects with normal glucose tolerance (NGT) and those with recently diagnosed T2DM. Additionally, we studied mechanisms related to BP behavior in subjects with different degrees of GT.

SUBJECTS AND METHODS

Subjects

This is a cross-sectional study of consecutive adult patients with abnormal glycemia (fasting or 2-hour glucose) and/or A1c measurement or with risk factors for the development of DM, such ashaving different components of the metabolic syndrome, family history of T2DM and sedentary lifestyle, referred for ambulatory care in the Metabolism Unit of Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul. Patients were enrolled from 2009 to 2016. Inclusion criteria included adults with age ≥18 years whose glycemic status was not previously defined. Exclusion criteria included clinically significant autoimmune diseases, uncompensated hypo or hyperthyroidism, malignant disease that may affect 5-year survival, stage IV or

V chronic kidney disease, acquired immune deficiency syndrome (AIDS), pregnancy/lactation, dementia, cirrhosis, hepatitis, alcohol or illicit drug abuse, glucocorticoid or anti-retroviral treatment, and malnutrition. The protocol was approved by the Hospital de Clínicas de Porto Alegre Institutional Review Board and the subjects provided written informed consent.

Study Procedures and Assays

Standing height (in centimeters; cm) and weight (in kilograms; kg) were measured in shoeless subjects wearing light clothes and were used to calculate body mass index as weight (kg) / height^2 (meters). Waist circumference was taken at the midpoint between the lower costal margin and the iliac crest measured to the nearest 0.5 cm.

A standard 75g oral glucose tolerance test (OGTT) was performed in the morning after a 12-hour overnight fast. Blood samples for measurements of glucose and insulin were drawn at fasting and every 30 minutes after glucose oral ingestion. A baseline blood sample was also drawn for lipid profile, glycated hemoglobin (A1c) and creatinine levels. Participants were instructed to collect a 24-hour urine sample. The urine was kept cold (4°C) until brought to the clinical visit. Subjects avoided intense physical activity during the collection period and urinary collection was postponed in case of fever, urinary tract infection or menstruation.

Plasma glucose was determinate by hexoquinase method, cholesterol and triglycerides by enzymatic colorimetric method, creatinine by Jaffé reaction (Advia 1800; Siemens Healthcare Diagnostics, Tarrytown, NY); insulin by quimioluminase method (Advia Centaur; Siemens Healthcare Diagnostics); UAE by

immunoturbidimetry; cortisol and ACTH by electrochemiluminescence and urinary metanephrines and A1c by HPLC method.

The CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration) was used to estimate glomerular filtrate rate: GFR = 141 * min (Scr/κ,1)$^\alpha$ * max (Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 [if female] * 1.159 [if black]. Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The methodology and procedures were reviewed in order to adequate to STROBE Statement.[26]

Determination of insulin sensitivity and resistance

Insulin sensitivity was assessed using Stumvoll Index (ISI) [0.226 – (0.0032 x BMI) – (0.0000645 x 2-h insulin (mmol/L)] – [0.00375 x 90 min glucose (mmol/L)] and insulin resistance by the homeostasis model assessment (HOMA-IR) [fasting glucose (mmol/L) x fasting insulin (μU/mL)] / 22.5)].

Classification of Glucose Tolerance

Using fasting and 2-hour plasma glucose concentrations, subjects were categorized based on the American Diabetes Association criteria as having normal glucose tolerance (NGT) [fasting plasma glucose (FPG) < 100 mg/dl and 2-h plasma glucose < 140 mg/dl)]; impaired fasting glucose (IFG; FPG 100 -125 mg/dl and 2-h plasma glucose < 140 mg/dl); impaired glucose tolerance (IGT; FPG < 100 mg/dl and 2-hr plasma glucose 140 - 199mg/dl), or diabetes (DM; FPG $\geq$ 126 mg/dl and 2-h

plasma glucose ≥ 200 mg/dl). We classified subjects with IFG and/or IGT as a unique group denominated impaired glucose metabolism (IGM). Subjects with DM were submitted to a second test to confirm diagnosis.

Blood pressure measurements

Blood pressure was measured one week after withdrawal from all medications with antihypertensive effect. Office BP was measured after 10min at rest, in the right arm, three times (1 minute interval between each measurement), using an oscillometric BP monitor (OMRON®, H-003D), with cuff adjusted for arm circumference. The mean of the last two measurements was used to estimate systolic and diastolic BP. Arterial hypertension was diagnosed if mean SBP ≥ 140mmHg and/or DBP ≥ 90mmHg in two different ocassions, or if patient was using antihypertensive treatment. [27]

ABPM was performed by oscillometric method (Spacelabs 90207, with validated certificate), with recordings taken every 15 min in daytime and every 20 min during night. ABPM was performed on an ordinary working day and patients were advised to maintain their usual daily activities. 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 tests had at least 80% success rate on BP measurements. The parameters evaluated were mean SBP and DBP 24-h, daytime and nighttime. Pulse pressure (difference between SBP and DBP) was recorded by 24-ABPM. Percentage of SBP and DBP nocturnal reduction (% reduction = 100* (1 – [mean nighttime BP/ mean daytime BP])) was evaluated and considered to classify subjects as dippers (reduction ≥ 10%) or nondippers (reduction < 10%). Morning SBP surge was defined as the early morning SBP (2-hour average of eight 15-min SBP readings just after wake-up) minus

the lowest nocturnal SBP (1-hour average of three 20-min SBP readings on the lowest nighttime reading).

According to the office and 24-hour ABPM measurements, BP status was classified into masked hypertension (office BP <140/90mmHg and ABPM daytime BP >130/85mmHg), white-coat hypertension (office BP ≥140/90mmHg and ABPM daytime BP ≤130/85mmHg) and sustained hypertension (office BP ≥140/90mmHg and ABPM daytime BP >130/85mmHg).[28]

Area under curve of the 24-h BP levels according to GT was calculated by the trapezoidal method. [29]

Data Analysis and Statistical Methods

Data was described as mean ± standard deviation (SD) or median (P25 - P75). Categorical data were compared by χ^2 test. Comparisons among glucose tolerance groups were performed by one-way ANOVA or Kruskal-Wallis tests, if variables were normal or non-normal distributed, respectively. Correlations were performed by Pearson's correlation test for normally distributed variables and by Spearman's test when at least one of the variables in the analysis had a skewed distribution.

To test the relationship between glucose tolerance status and 24-h systolic blood pressure by ABPM and pulse pressure we built models using the general estimating equation approach. This model allows including subjects who had missing time points of blood pressure measurements within an hour interval along the 24-h ABPM. Five different general estimation equation regression models were built using as independent variables those that were considered to have a plausible biological effect on blood pressure levels and/or more significant correlation with blood pressure levels in

univariate models based on the value of the correlation coeffcient. While the first was a crude model, the second model was adjusted by gender and age. Model 3 added waist circumference to model 2. Model 4 added 24-h urinary albumin excretion to model 3. The last model added years of education and serum cortisol levels to model 4, since these variables showed significant and important correlations with 24-h blood pressure in univariate analysis. Bonferroni *post-hoc* test was applied for comparison among different glucose tolerance status categories.

We also used multiple linear regression analyzes to determine factors related to 24-h blood pressure measurements (dependent variable) using the area under the curve of 24-h blood pressure by the trapezoid method, since this estimate has been shown to present a better correlation of possible determinants of 24-h BP measurements. [30]

Sample size calculation was performed with G Power 3.1.9.2. Considering acceptable a power of 80% and an α error of 5%, we calculated an effect size of 0.31, suggesting medium effect to compare blood pressure parameters of subjects with different degrees of glucose tolerance. For the multiple regression analysis, and taking in account a correlation coefficient of 0.36 for a medium effect, it would be necessary to compare 98 individuals with different degrees of glucose tolerance to analyze differences in their blood pressure parameters.

A two-sided P value < 0.05 was considered significant. Statistical analysis was performed using the Statistical Package for the Social Science program (SPSS, version 18.0 for Windows, Chicago, IL).

RESULTS

Subject characteristics

The study group comprised 138 subjects, of whom 45 (32.6%) were males and 93 (67.3%) were females.

Clinical and laboratory characteristics are summarized in Table 1. Subjects were subdivided by glucose tolerance in NGT (n = 39; 28.2 %), IGM (n = 55; 39.8 %) and DM (n = 44; 31.8%). Subjects with NGT were younger than subjects with IGM and DM. By definition, subjects with IGM and DM had higher A1c, fasting and 2-h plasma glucose levels than subjects with NGT. These three groups did not differ by gender distribution, years of schooling, smoking status, eGFR, insulin, cortisol, ACTH levels, and the 24-h urinary levels of normetanephrines and metanephrines. While BMI, WC, US-CRP, UAE, and HOMA-IR increased with decreasing GT, Stumvoll ISI decreased with progressive hyperglycemia. Total cholesterol was significantly higher in subjects with IGM than in the other two groups. Triglycerides, HDL and LDL-cholesterols did not differ by groups. Antihypertensive treatment scheme, which was stopped one week before data collection, was not different among groups (Table 1).

Office and ambulatory blood pressures and pulse pressure according to groups with different degrees of glucose tolerance

Blood pressure parameters according to GT are summarized in Table 2. A total of 65.9% subjects had office hypertension. These rates were higher in those with IGM and DM than those with NGT (NGT: 43.5% vs. IGM: 74.5% vs. DM 75.0%; P = 0.002). The prevalence of white-coat hypertension, sustained hypertension and masked hypertension were, respectively, of 17%, 48% and 5.8% and their rates were different among subjects with different degrees of glucose tolerance. Among these individuals,

68.1% subjects presented a nondipper profile of SBP. Nocturnal BP reduction and morning surge did not differ among groups (Table 2).

While the office SBP levels increased from NGT to DM, the DBP levels did not differ by glucose tolerance status. Office SBP did not differ between IGM and DM. By ABPM, 24-h, daytime and nighttime SBP levels progressively increased from NGT to DM. Diastolic blood pressure levels had the same pattern by daytime, nighttime and 24-h, however these differences did not reach statistical significance. Pulse pressure increased from NGT to DM (Table 2).

Relationship of demographic, clinical and laboratory characteristics with blood pressure parameters

Age (r = 0.317; P < 0.001), BMI (r = 0.182; P = 0.036), WC (r = 0.194; P = 0.028), FPG (r = 0.219; P < 0.001), 2-h plasma glucose (r = 0.316; P < 0.001), A1c (r = 0.193; P = 0.027), plasma cortisol (r = 0.263; P = 0.003), and 24-h UAE (r = 0.313; P < 0.001) were positively related to 24-h SBP, whereas years of schooling (r = -0.321; P < 0.001), ISI Stumvoll (r = -0.319; P <0.001) and eGFR (r = -0.177; P = 0.044) were inversely related to it. No significant correlations were observed between 24-h SBP and HOMA-IR (r = 0.097; P = 0.257), total cholesterol (r = 0.127; P = 0.140), HDL-cholesterol (r = 0.059; P = 0.499), LDL-cholesterol (r = 0.123; P = 0.188), triglycerides (r = 0.118; P = 0.171), US-CRP (r = 0.142; P = 0.100), ACTH (r = 0.139; P = 0.118), 24-h urinary metanephrines (r = 0.140; P = 0.180) and 24-h urinary normetanephrines (r = 0.052; P = 0.622.

24-h DBP was positively related to plasma cortisol (r = 0.205; P = 0.022) and 24-h UAE (r = 0.207; P < 0.023), whereas was inversely related to years of education (r = -0.238; P = 0.006). There was no relationship between 24-h DBP age, BMI, WC,

FPG, 2-h plasma glucose, A1c, ISI Stumvoll, HOMA-IR, eGFR, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, US-CRP, ACTH, 24-h urinary metanephrines and 24-h urinary normetanephrines (data not shown).

Modeling the blood pressure circadian rhythm according to glucose tolerance status

The circadian BP and PP profiles according to GT were respectively described in Figures 1, 2 and 3. Each hour includes the mean values of 3 or 4 measurements obtained by 24-hours ABPM of patients from each GT group. A total of 3239 measurements of mean hourly BP were used to develop the blood pressure rhythm curves according to GT (NGT: 908; IGM: 1284; DM: 1047).

Based on the fact that several demographic, clinical and laboratory characteristics were related to 24-h SBP, but not to 24-h DBP, we will show the analysis of the relationship between these characteristics and 24-h SBP. We performed a generalized estimating equation (GEE) model adjusted for potential confounders to determine the pattern of BP levels (systolic and diastolic) distribution over 24h according to glucose tolerance status. With this statistical approach we were able to analyze periods with missing data regarding blood pressure behavior along the 24-hs by ABPM. Models adjusted for gender, age, waist circumference, 24-h UAE, years of schooling and serum cortisol showed that 24-h SBP levels were higher in individuals with DM, compared to NGT, while IGM levels did not significantly differed from those in subjects with NGT nor DM groups (see Table 3). The same models were used to compare DBP levels among groups and it did not show statistical differences among them (data not shown).

GEE models were also performed to compare groups by PP levels. Even adjusting for age, gender, WC, 24-h UAE, years of schooling and serum cortisol, PP levels were significantly different between subjects with NGT and DM. Different models showed that PP increased with decreasing glucose while adjusting by age, sex and UAE. There was also a trend for PP be different in those with PDM compared to those with NGT and DM while also adjusting for WC, cortisol levels and years of education (see Table 3).

After showing that 24-hour SBP levels increased with decreasing GT, we examined how the area under the curve of 24-hour SBP might be actually related with GT, independently of central adiposity (waist circumference) and/or UAE. Multiple linear regression models were performed and GT showed to be the most important determinant of 24-h SBP, even after adjustments for gender, age, WC, UAE, years of schooling and serum cortisol (Table 4).

DISCUSSION

Previous studies reported the association between abnormalities of glucose metabolism and increased blood pressure levels.[13,31,32] However, few data are available about how BP levels behave along 24 hours of the day in subjects at high risk of developing DM. In our study, we have demonstrated that ambulatory BP levels increases with decreasing of GT and that subjects with IGM have abnormalities of BP homeostasis. By office measurements, subjects with IGM and DM had similar BP levels. Only by ABPM we were able to show that there are significant differences in the circadian rhythm of BP resulting in a distinct behavior in subjects with abnormal glucose metabolism, compared to those with NGT and those with DM.

Ayala et al. evaluated 12.765 hypertensive subjects of both gender, with and without T2DM, submitted to 48-h ABPM and showed that subjects with diabetes (n=2954) had higher SBP and higher PP levels, independently of the presence or absence of pharmacologic anti-hypertensive treatment at the time of these measurements.[23] We have also found that 24-h SBP levels and PP were higher in both IGM and DM groups compared to those with NGT corroborating their findings.

Putz et al. submitted 75 subjects with impaired glucose tolerance (IGT) and 40 healthy volunteers to 24-h ambulatory blood pressure monitoring (ABPM). Subjects with IGT showed higher levels of 24 hours, daytime and nighttime systolic and diastolic BP levels, even after adjustment for body mass index and cardiovascular autonomic neuropathy.[21] In another study, abnormalities of BP homeostasis were evaluated by 7-days ABPM in 12 obese subjects at screening for a weight loss trial. Subjects with PDM (n = 6; impaired fasting glucose and/ or IGT) have shown elevated mean BP levels than subjects without PDM.[20] Finally, rats submitted to a low vs. high glycemic index diets have shown a different behavior of BP. Those who developed abnormalities of glucose metabolism and systemic inflammation developed an abnormal circadian BP behavior than those who did not develop these abnormalities. [22] Cardoso et al. evaluated by 24-h ABPM 391 subjects with T2DM, without and with initial and severe cardiovascular dysautonomia and showed higher SBP and PP according to the worsening of the autonomic neuropathy.[33] These data suggests that subjects with abnormal glucose metabolism, even in its early stage of PDM, are at high risk of developing abnormalities of the circadian BP rhythm. Additionally, a wide PP may be the result of an earlier disruption of the autonomic nervous system, which has been already identify as a factor that is related to these abnormalities in subjects with diabetes.

In our study, years of schooling was inversely related to BP levels while adjusting for other possible determinants by uni and multivariable analyses. Previous data already demonstrated an inverse relationship between education level and BP levels. [34,35] This finding reinforce strategies to plan studies to better understand mechanisms and possible interventions to counteract the effect of low education on behaviors that leads the more vulnerable PDM population to develop abnormalities of blood pressure homeostasis leading to BP hypertension, micro and macrovascular complications [36].

Blood pressure measurement by 24-h ABPM is a well-established method with determined cut-off values for the identification of abnormalities of BP not possible to be detected in the office. However, data regarding the relationship between BP abnormalities and the development of micro and macrovascular complications in subjects with PDM is poorly known. Salles et al. studied the association between office and ambulatory BP levels and vascular complications in subjects with DM and showed that ambulatory BP levels better correlated to T2DM vascular complications than office BP levels.[37] It is already established that PDM is related to the same chronic microvascular complication of DM.[2-5] Our study showed an increase in 24-h blood pressure levels according to the decrease of GT. Although interventional studies needs to be planned to test this hypothesis, this data may suggest physicians to have more attention in care of BP in subjects with PDM.

On previous studies a nondipping nocturnal pattern of BP was more frequently identified in subjects with DM.[23] However, few data is available about the behavior of BP at night in subjects with earlier abnormalities of glucose metabolism. Putz et al. reported a 66.7% prevalence of non-dipping in subjects with IGT, similarly to our finding of 67.3% in those with IGM.[21] Another study demonstrated that non-dippers

subjects with essential hypertension were more glucose intolerant than dippers, suggesting the relationship between abnormalities of glucose metabolism and abnormalities of the circadian rhythm of BP even before the development of DM.[31]

Elevation of PP is considered an indirect marker of loss of the arterial elasticity.[38] Elevated PP levels in subjects with diabetes obtained in the office and by ABPM have been related to high cardiovascular risk and also to the development of macro and microvascular complications. [39-41] Few data is available about the relationship between high PP levels and PDM. Our study showed that PP levels increases with decreasing GT.

This study has potential limitations to be commented. As a cross-sectional observational study, data obtained allowed us to identify factors related to circadian BP abnormalities that may happen in an earlier phase of glucose metabolism deregulation, namely PDM. However, it is not possible to infer a cause consequence relationship. Although we were not able to definitely study the contribution of autonomous nervous system dysautonomia in leading to blood pressure circadian rhythm abnormalities by gold standard investigational methods, we used the catecholamines metabolites 24-h urinary normetanephrines and metanephrines as markers of this activity, and we did not find a correlation of these surrogates markers with abnormalities of blood pressure homeostasis. In fact, we did not find differences in the urinary levels of these metabolites of catecholamines in subjects compared subjects with different degrees of glucose tolerance. The ABPM may be a more reliable measurement of blood pressure if performed for more prolong time and would bring a more clear understanding of our findings due to a more realistic and precise evaluation of blood pressure.[20,24] However, all ABPM tests and office BP measurements were obtained while stopping anti-hypertensive agents one week before data collection and we were able to perform our

analyses without the interference of medications that would change blood pressure measurements. Additionally, our sample was composed of consecutive subjects that were referred to our clinic without a previously definition of GT which reduce the chance of selection and sample bias.

In conclusion, this study provides evidence that subjects with PDM, a state of earlier abnormalities of glucose regulation, may have abnormalities of BP homeostasis that are possible to be found with ABPM, but not with office BP measurements. Prospective observational and interventional studies needs to be designed to confirm these findings and to understand how these abnormalities are related to the development of high BP, micro and macrovascular complications of DM. A more clear picture of how we could intervent regulating blood pressure homeostasis in subjects with earlier abnormalities of glucose metabolism may be a fundamental point of care to create new strategies to control BP on these population at risk for cardiovascular diseases.

Table 1. Baseline characteristics of subjects with different degrees of glucose tolerance

	NGT (n = 39)	IGM (n = 55)	DM (n = 44)	P
Age (years)	47.9 ± 14.4	56.6 ± 10.4	53.6 ± 12.3	0.002
Female – n (%)	29 (74.4)	43 (78.2)	27 (61.4)	0.166
Education (years of schooling)	9 (5 -12)	8 (5 – 12)	8 (4 – 11)	0.835
Smokers – n (%)	4 (10.2)	5 (9.1)	8 (18.1)	0.401
Body mass index (kg/m^2)	29.3 ± 4.7	31.3 ± 6.4	33.6 ± 6.5	0.009
Waist circumference (cm)	93.8 ± 11.3	105.5 ± 12.6	109.2 ± 14.3	<0.001
Antihypertensive treatment – n (%)	11 (28.2)	27 (49.0)	20 (45.4)	0.083
ACE inhibitor – n (%)	4 (10.2)	16 (29.0)	8 (18.1)	0.129
AR blockers – n (%)	1 (2.5)	2 (3.6)	1 (2.2)	0.959
Diuretics – n (%)	3 (7.6)	14 (25.4)	9 (20.4)	0.105
Beta-blockers – n (%)	4 (10.2)	9 (16.3)	3 (6.8)	0.433
Calcium channel blockers	2 (5.1)	5 (9.0)	3 (6.8)	0.825
Triglycerides (mg/dl)	105 (69 – 147)	133 (107 – 191)	120 (91 – 173)	0.080
Total cholesterol (mg/dl)	197.0 ± 37.3	214.4 ± 45.0	192.4 ± 36.8	0.020
HDL-cholesterol (mg/dl)	49.0 ± 13.2	48.2 ± 12.5	46.8 ± 11.1	0.718

LDL-cholesterol (mg/dl)	124.1 ± 31.8	132.4 ± 38.9	116.8 ± 31.1	0.143
Fasting plasma glucose(mg/dl)	89 (83 – 93)	103 (94 – 110)	122 (110 – 204)	-
2-h plasma glucose (mg/dl)	106 (91 – 121)	160 (150 – 176)	220 (258 – 374)	-
A1c (%)	5.4 ± 0.35	6.0 ± 0.62	7.4 ± 1.9	<0.001
HOMA-IR	1.94 (1.1 – 2.9)	2.9 (1.7 – 4.3)	4.3 (3.0 – 8.8)	<0.001
Stumvoll insulin sensitivity index	0.10 (0.09 – 0.12)	0.08 (0.07 – 0.09)	0.05 (0.02 – 0.07)	<0.001
US - CRP(mg/l)	1.7 (0.7 – 2.9)	4.2 (1.2 – 10.3)	3.5 (1.5 – 13.7)	0.001
Plasma cortisol (µg/dl)	12.3 (10.9 – 13.9)	14.2 (10.0 – 18.7)	14.5 (10.4 – 18.0)	0.233
ACTH (pg/ml)	20.7 (15.2 – 33.5)	22.8 (14.3 – 30.4)	24.0 (17.3 – 33.9)	0.537
eGFR (CKD-EPI; ml/min/m^2)	94.4 ± 19.4	88.0 ± 19.6	93.7 ± 17.9	0.217
24-h UAE (mg/24h)	1.0 (0.0 – 7.2)	4.3 (1.0 – 8.4)	7.0 (1.0 – 21.3)	0.015
24-h urinary normetanephrines (µg/24h)	238.3 (138.5 – 426.0)	262.5 (182.0 – 416.0)	249.8 (132.5 – 377.5)	0.618
24-h urinary metanephrines (µg/24h)	78.0 (35.5 – 103.1)	69.5 (46.7 – 100.2)	71 (36.5 – 118.5)	0.894

Data described as mean ± standard deviation or median (P25 - P75).

NGT: normal glucose tolerance; IGM: impaired glucose metabolism; DM: diabetes mellitus; ACE: angiotensin-converting enzyme;

AR: angiotensin II receptor; US-CRP: ultra sensitive C-reactive protein ; ACTH: adrenocorticotropic hormone;

eGFR: estimated glomerular filtration rate; UAE: urinary albumin excretion

Table 2. Office and ambulatory blood pressure parameters according to glucose tolerance status

	NGT (n = 39)	IGM (n = 55)	DM (n = 44)	P
Office hypertension – n (%)	17 (43.5)	41 (74.5)	33 (75.0)	0.002
White-coat hypertension – n (%)	3 (7.6)	14 (25.4)	7 (15.9)	-
Sustained hypertension – n (%)	14 (35.8)	27 (49.0)	26 (59.0)	-
Masked hypertension – n (%)	1 (2.5)	5 (9.0)	2 (4.5)	-
Office BP				
SBP (mmHg)	130.8 ± 21.8	142.6 ± 22.4	142.7 ± 25.6	0.036
DBP (mmHg)	82.9 ± 13.1	86.8 ± 11.8	83.1 ± 14.3	0.271
24 hour pulse pressure (mmHg)	45.8 ± 8.4	52.3 ± 10.6	57.06 ± 11.8	<0.001
24 hour BP				
SBP (mmHg)	122. ± 15.1	129.0 ± 14.6	135.4 ± 17.3	0.001
DBP (mmHg)	76.3 ± 10.5	77.0 ± 10.3	77.4 ± 10.8	0.662
Daytime BP				
SBP (mmHg)	125.4 ± 15.7	132.1 ± 14.9	138.3 ± 17.0	0.001
DBP (mmHg)	79.8 ± 11.1	80.2 ± 10.8	81.5 ± 10.9	0.771
Nighttime BP				
SBP (mmHg)	114.4 ± 14.9	122.6 ± 15.7	129.0 ± 18.8	0.001

DBP (mmHg)	67.7 ± 10.3	70.3 ± 11.1	72.2 ± 12.0	0.214
Nocturnal BP reduction				
SBP (%)	8.1 (4.7 – 12.7)	6.7 (2.9 – 12.1)	6.4 (3.4 – 10.0)	0.472
DBP (%)	14.8 (7.9 – 19.7)	12.5 (6.2 – 18.1)	10.4 (7.1 – 17.4)	0.315
Non-dippers SBP – n (%)	24 (62.3)	37 (67.3)	33 (75.0)	0.495
Morning surge				
SBP (mmHg)	10.7 (5.2 – 16.6)	10.7 (0.8 – 22.1)	11.7 (1.25 – 22.3)	0.946
DBP (mmHg)	13.2 (6.0 – 17.2)	15.0 (3.8 – 21.7)	14.5 (6.6 – 20.0)	0.959

** Non-dippers (day-night change in systolic blood pressure ≤ 10%)

BP: blood pressure; SBP: Systolic blood pressure; DBP: diastolic blood pressure; NGT: normal glucose tolerance;

IGM: impaired glucose metabolism; DM: diabetes mellitus

Table 3. Generalized estimating equation models to investigate factors related to 24-hour systolic blood pressure, 24-hour pulse pressure and their relationship with glucose tolerance status

24-hour systolic blood pressure						
Model	Comparisons	Mean difference	Std. error	P	95% CI	
Crude	NGT vs. IGM	-7.73	3.07	**0.036**	-15.08	-0.37
	NGT vs. DM	-13.58	3.50	**<0.001**	-21.96	-5.19
	IGM vs. DM	-5.80	3.22	0.208	-13.56	1.86
Gender + age	NGT vs. IGM	-4.80	3.18	0.394	-12.42	2.81
	NGT vs. DM	-10.87	3.37	**0.004**	-18.94	-2.80
	IGM vs. DM	-6.06	3.18	0.169	-13.68	1.54
Gender + age + WC	NGT vs. IGM	-3.38	3.30	0.918	-11.29	4.53
	NGT vs. DM	-9.36	3.65	**0.031**	-18.11	-0.62
	IGM vs. DM	-5.98	3.23	0.193	-13.73	1.76
Gender + age + 24-h UAE	NGT vs. IGM	-6.77	3.43	0.145	-14.99	1.44
	NGT vs. DM	-13.60	3.57	**<0.001**	-22.16	-5.04

Model	Comparisons	Mean difference	Std. error	P	95% CI	
	IGM vs. DM	-6.83	3.52	0.159	-15.28	1.61
Gender + age + 24-h UAE + WC	NGT vs. IGM	-4.75	3.45	0.506	-13.02	3.51
	NGT vs. DM	-11.11	3.80	**0.010**	-20.22	-2.00
	IGM vs. DM	-6.35	3.50	0.209	-14.74	2.03
Gender + age + 24-h UAE + WC + years of schooling + serum cortisol	NGT vs. IGM	-5.82	3.47	0.283	-14.14	2.50
	NGT vs. DM	-12.14	4.41	**0.018**	-22.70	-1.55
	IGM vs. DM	-6.32	3.76	0.278	-15.33	2.67

24-hour pulse pressure						
Model	Comparisons	Mean difference	Std. error	P	95% CI	
Crude	NGT vs. IGM	-6.72	1.97	**0.002**	-11.45	-1.98
	NGT vs. DM	-11.39	2.21	**<0.001**	-16.69	-6.09
	IGM vs. DM	-4.67	2.28	0.122	-10.14	0.79
Gender + age	NGT vs. IGM	-4.49	2.03	0.081	-9.35	0.37
	NGT vs. DM	-9.90	2.16	**<0.001**	-15.08	-4.72
	IGM vs. DM	-5.41	2.25	**0.049**	-10.81	-0.01

Gender + age + WC	NGT vs. IGM	-2.41	2.24	0.846	-7.79	2.96
	NGT vs. DM	-7.58	2.31	**0.003**	-13.11	-2.05
	IGM vs. DM	-5.16	2.19	0.055	-10.41	0.08
Gender + age + 24-h UAE	NGT vs. IGM	-5.25	2.12	**0.040**	-10.33	-0.18
	NGT vs. DM	-11.17	2.31	**<0.001**	-16.72	-5.62
	IGM vs. DM	-5.91	2.61	0.007	-12.18	0.35
Gender + age + 24-h UAE	NGT vs. IGM	-3.10	2.31	0.540	-8.66	2.44
+ WC	NGT vs. DM	-8.51	2.40	**0.001**	-14.27	-2.76
	IGM vs. DM	-5.40	2.49	0.090	-11.37	0.55
Gender + age + 24-h UAE	NGT vs. IGM	-3.80	2.38	0.334	-9.52	1.91
+ WC + years of schooling	NGT vs. DM	-9.66	2.77	**0.002**	-16.31	-3.01
+ serum cortisol	IGM vs. DM	-5.85	2.73	0.097	-12.41	0.69

WC: waist circumference; UAE: urinary albumin excretion; NGT: normal glucose tolerance;

IGM: impaired glucose metabolism; DM: diabetes mellitus

Table 4. Multiple linear regression analysis to investigate factors related to 24-hour systolic

blood pressure area under de curve and their relationship with glucose tolerance status

Model	Independent variables	R	β	Partial r value	P
1	Glucose tolerance	0.379	123.78	0.243	**0.012**
2	Glucose tolerance	0.373	113.51	0.202	**0.040**
	Waist circumference		1.20	0.042	0.671
3	Glucose tolerance	0.411	164.13	0.309	**0.003**
	24-h UAE		- 0.150	- 0.078	0.461
4	Glucose tolerance	0.424	140.14	0.249	**0.017**
	Waist circumference		3.23	0.283	0.114
	24-h UAE		- 0.175	- 0.091	0.393
5	Glucose tolerance	0.536	151.81	0.264	**0.018**
	Waist circumference		3.27	0.122	0.281
	24-h UAE		- 0.288	- 0.158	0.160
	Years of schooling		- 26.74	- 0.288	**0.009**
	Serum cortisol		13.33	0.206	0.066

All models were adjusted by gender and age. UAE: urinary albumin excretion
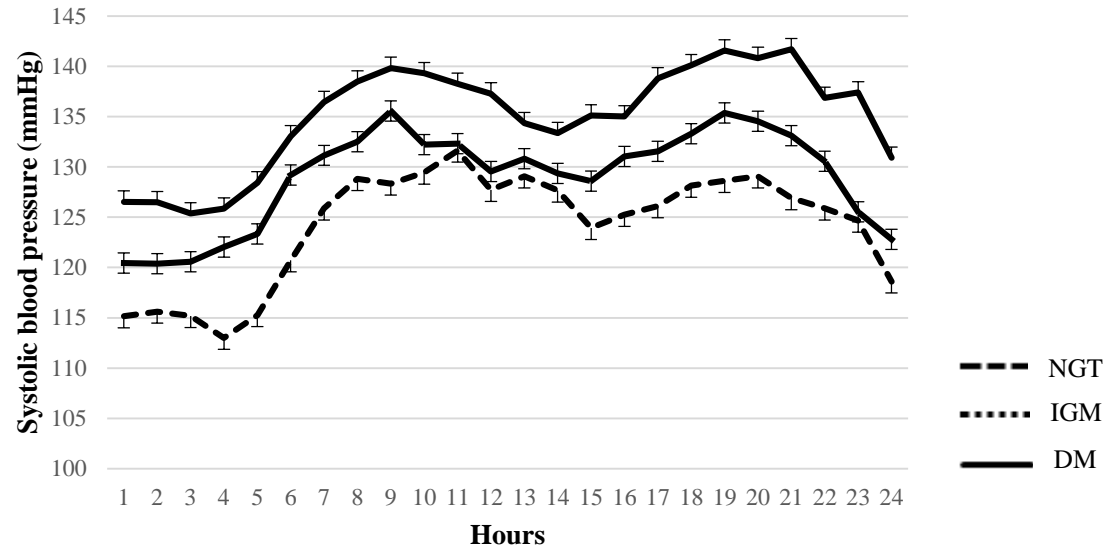
Figure 1. 24-Hour systolic blood pressure in subjects with different degrees of glucose tolerance

NGT: normal glucose tolerance; IGM: impaired glucose metabolism; DM: diabetes mellitus
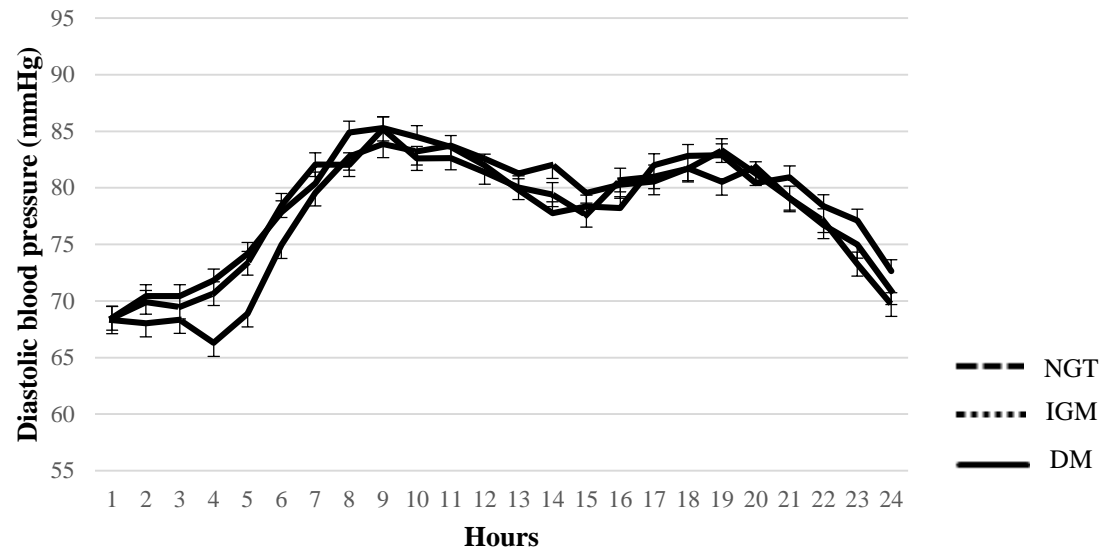
Figure 2. 24-Hour diastolic blood pressure in subjects with different degrees of glucose tolerance

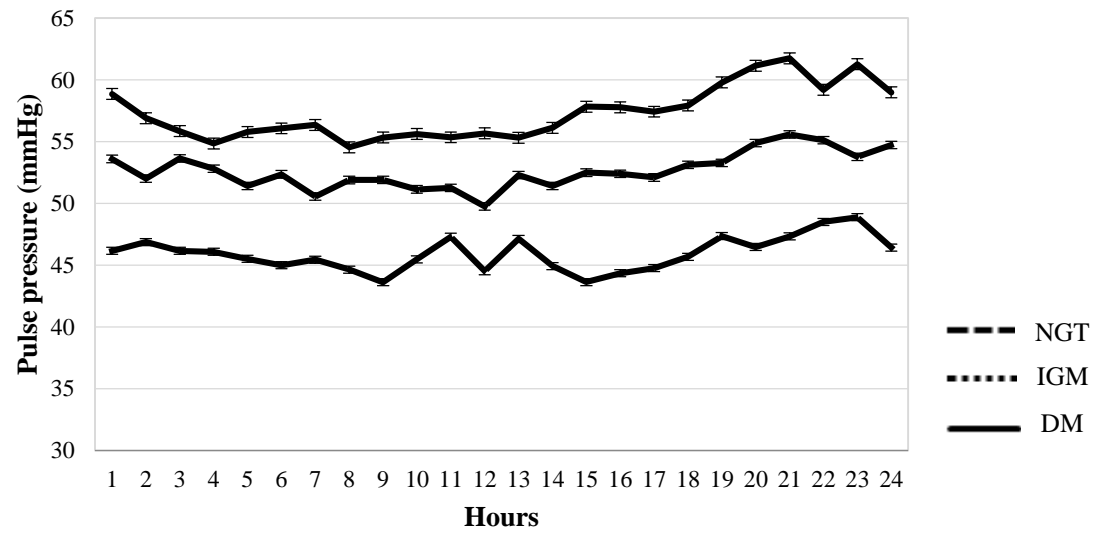NGT: normal glucose tolerance; IGM: impaired glucose metabolism; DM: diabetes mellitus

Figure 3. 24-Hour pulse pressure in subjects with different degrees of glucose tolerance

NGT: normal glucose tolerance; IGM: impaired glucose metabolism; DM: diabetes mellitus

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IV - CONSIDERAÇÕES FINAIS

O pré-diabetes apresenta elevada prevalência em adultos e está relacionado às mesmas complicações crônicas micro e macrovasculares encontradas em indivíduos com diabetes.

Indivíduos com diabetes apresentam anormalidades da homeostase pressórica que habitualmente estão relacionadas com maior risco de desenvolvimento de complicações vasculares. Entretanto, o comportamento da homeostase pressórica em indivíduos com pré-diabetes é pouco estudado. O melhor entendimento do ritmo circadiano da pressão arterial nesta população de risco para o desenvolvimento de diabetes é fundamental para que possam ser elaboradas estratégias de prevenção primária do desenvolvimento de complicações vasculares que carregam consigo altas taxas de morbidade e mortalidade.

Este estudo é o primeiro a avaliar a relação das anormalidades do ritmo circadiano da pressão arterial comparando indivíduos com normoglicemia, pré-diabetes e diabetes. Através da avaliação da monitorização ambulatorial da pressão arterial de 24 horas em 138 indivíduos foi possível demonstrar que a glicemia apresenta importante relação com o aumento dos níveis de pressão arterial. Demontrou-se que há um aumento destes conforme a piora da tolerância à glicose mesmo após ajustes para fatores que podem determinar anormalidades da homeostase da pressão arterial. Estudos prospectivos são necessários para a confirmação destes achados e para avaliar a implicância da desregulação da homeostase pressórica que ocorre no pré-diabetes na fisiopatogênese das complicações do diabetes.