Carlos Alberto Mourão Júnior

ASPECTOS DO CONTROLE METABÓLICO EM PACIENTES ADULTOS PORTADORES DE DIABETES MELITO, EM USO DE INSULINA, ATENDIDOS EM UM CENTRO ESPECIALIZADO DO SISTEMA ÚNICO DE SAÚDE

TESE apresentada à Universidade Federal de São Paulo – Escola Paulista de Medicina, para obtenção do Título de Doutor em Ciências.

Orientador: Prof. Dr. Sérgio Atala Dib
Co-orientador: Dr. João Roberto de Sá

São Paulo
2006

Mourão Júnior, Carlos Alberto
Aspectos do controle metabólico em pacientes adultos portadores de diabetes melito, em uso de insulina, atendidos em um centro especializado do Sistema Único de Saúde / Carlos Alberto Mourão Júnior. -- São Paulo, 2006.
vii, 52f

Tese (Doutorado) – Universidade Federal de São Paulo. Escola Paulista de Medicina. Programa de Pós-graduação em Endocrinologia.

Título em inglês: Aspects of the metabolic control in adult diabetic patients on insulin at an outpatient diabetes center in Brazil

1. Diabetes mellitus. 2. Insulina. 3. Metformina.
4. Síndrome metabólica.

"The most beautiful thing we can experience is the mysterious. It is the source of all true art and science. He to whom this emotion is a stranger, who can no longer pause to wonder and stand rapt in awe, is as good as dead: his eyes are closed."

— ALBERT EINSTEIN

ATA DE APROVAÇÃO

Serviço Público Federal
Universidade Federal de São Paulo
Escola Paulista de Medicina
Pró-Reitoria de Pós-Graduação e Pesquisa
Rua Pedro de Toledo, 943 - CEP 04039-002
Vila Clementino - São Paulo - SP - Brasil
Tel.: (55-11) 5579-5700 - Fax.: (55-11) 5579-6481

UNIFESP

ATA DA REUNIÃO DA COMISSÃO JULGADORA DA DEFESA DE TESE DE DOUTORADO

Aos trinta e um dias do mês de março do ano dois mil e seis, reuniu-se no Anfiteatro Nylceo Marques de Castro às 9:00 horas, a Comissão Julgadora para a DEFESA DE TESE DE DOUTORADO , solicitada por CARLOS ALBERTO MOURÃO JÚNIOR, aluno(a) do Programa de Pós-Graduação em ENDOCRINOLOGIA CLÍNICA, que apresentou tese sob o Título: ASPECTOS DO CONTROLE METABÓLICO EM PACIENTES ADULTOS PORTADORES DE DIABÉTICOS MELITO, EM USO DE INSULINA, ATENDIDOS EM UM CENTRO ESPECIALIZADO DO SISTEMA ÚNICO DE SAÚDE.
A referida Comissão esteve constituída pelos Professores Doutores:

Prof. Dr. ANTONIO CARLOS PIRES - Professor Adjunto - Medicina - Faculdade de Medicina de São José do Rio Preto;
Prof. Dr. JOÃO ROBERTO DE SÁ - Doutor em Medicina - Disciplina de Endocrinologia - Universidade Federal de São Paulo - Escola Paulista de Medicina;
Prof. Dr. ORSINE VALENTE - Professor Adjunto - Disciplina de Endocrinologia - Faculdade de Medicina da Fundação Universitária do ABC;
Prof. Dr. SERGIO ATALA DIB - Professor Adjunto - Disciplina de Endocrinologia - Universidade Federal de São Paulo - Escola Paulista de Medicina;
Prof. Dr. SIMAO AUGUSTO LOTTEMBERG - Professor Doutor - Disciplina de Endocrinologia - Universidade de São Paulo - Faculdade de Medicina;

O(a) Presidente Prof. Dr. SERGIO ATALA DIB , inicia a sessão dando a palavra ao(a) candidato(a), que dispõe de trinta minutos no máximo, para expor sua tese. A seguir dá a palavra aos Professores para a arguição. Cada examinador(a) dispõe de trinta minutos, no máximo, para arguição, bem como o(a) candidato(a) para as respostas. Tendo o(a) candidato(a) respondido todas as arguições em tempo hábil os membros da Banca Examinadora , emitiram seus Pareceres:

Prof. Drs. :
ANTONIO CARLOS PIRES, APROVADO.
JOÃO ROBERTO DE SÁ, APROVADO
ORSINE VALENTE, APROVADO
SERGIO ATALA DIB, APROVADO
SIMAO AUGUSTO LOTTEMBERG, APROVADO

Em face dos referidos pareceres, a Comissão Julgadora considera o(a) Sr(a) CARLOS ALBERTO MOURÃO JÚNIOR habilitado(a) a receber o título de DOUTOR EM CIÊNCIAS pela UNIVERSIDADE FEDERAL DE SÃO PAULO - Escola Paulista de Medicina. E por estarem de acordo, assinam a presente ata. São Paulo, sexta-feira, 31 de março de 2006.

Prof. Dr. ANTONIO CARLOS PIRES

Prof. Dr. JOÃO ROBERTO DE SÁ

Prof. Dr. ORSINE VALENTE

Prof. Dr. SERGIO ATALA DIB

Prof. Dr. SIMAO AUGUSTO LOTTEMBERG

Sugestões e Observações

Agradecimentos

Ao Prof. Dr. Sérgio Atala Dib e ao Prof. Dr. João Roberto de Sá, orientadores e amigos, pela oportunidade e confiança em mim depositada e pela participação fundamental em todas as etapas desse trabalho;

Ao Programa de Pós-graduação em Endocrinologia da UNIFESP, em especial à Prof. Ieda Therezinha do Nascimento Verreschi e à Sra. Amaryllis Cândida Salzano, pela gentil acolhida e apoio;

Ao Serviço de Controle de Hipertensão Diabetes e Obesidade, da Secretaria de Saúde de Juiz de Fora, em especial à Enfermeira Lúcia Helena Delgado de Souza, por todo o apoio prestado;

À Dra. Olívia Maria Silveira Guedes, médica da Universidade Federal de Juiz de Fora, por sua ajuda na coleta e organização dos dados desse trabalho;

Ao amigo e colega Dr. Gustavo Andrade de Paulo, pelo apoio e colaboração;

À minha mãe, Maria da Glória Mouty de Paula Mourão, a quem tudo devo; e à memória de meu pai, Carlos Alberto Mourão, cujos exemplos de probidade continuam a me nortear pela vida afora;

Ao meu primo Christiano de Paula Haddad, que como um pai me auxiliou viabilizando minha formação médica;

À memória de dois grandes mestres que me servem de exemplo: Prof. Rubens Metello de Campos e Prof. Jacy Ribeiro Azevedo da Silva;

Aos pacientes diabéticos, que carregando o fardo de sua enfermidade, contribuem anonimamente para a ciência na esperança de um futuro melhor;

A Deus, pela oportunidade de lutar no árduo rito de evolução terrena.

Sumário

Agradecimentos iii

Resumo v

Abstract v

1 INTRODUÇÃO 1

2 PRIMEIRO ARTIGO 5

3 SEGUNDO ARTIGO 25

4 CONSIDERAÇÕES FINAIS 32

5 CONCLUSÕES 34

6 ANEXO 35

7 REFERÊNCIAS BIBLIOGRÁFICAS 44

Resumo

O presente estudo analisa o perfil de pacientes diabéticos adultos do tipo 1 e do tipo 2, usuários de insulina, em uma amostra de uma cidade brasileira (Juiz de Fora - MG), com o objetivo de avaliar suas características epidemiológicas e o controle metabólico alcançado. Foram analisados os prontuários de pacientes diabéticos de um serviço especializado em usuários de insulina no município de Juiz de Fora (MG). Foram separados dois grupos: 175 prontuários referentes aos diabéticos do tipo 1 (avaliando o impacto do atendimento multidisciplinar no controle glicêmico) e 57 prontuários referentes aos diabéticos do tipo 2 que passaram a utilizar metformina associada à insulinoterapia (avaliando a ação da metformina nos controles glicêmico e lipídico, bem como na pressão arterial). O estudo concluiu que pacientes diabéticos do tipo 1 atendidos em um centro multidisciplinar apresentaram um melhor controle glicêmico, e que a associação da metformina à insulina ocasionou melhora dos níveis de colesterol total e do controle glicêmico dos pacientes diabéticos do tipo 2 com síndrome metabólica.

Abstract

The present study analyzes the type 1 and type 2 adult diabetic on insulin patients' profile in a sample of a Brazilian city (Juiz de Fora), aiming to evaluate their characteristics and the reached metabolic control. The patients' records of patients from a multidisciplinary diabetes center in a Brazilian city (Juiz de Fora) were analyzed. They were separated in two groups: 175 records regarding the diabetics of the type 1 (evaluating the impact of the multidisciplinary service approach to the glycemic control) and 57 records regarding the diabetics of the type 2 that started to use metformin associated to insulin (evaluating the action of the metformin in the glycemic and lipidic control, as well as in the blood pressure). The study concluded that type 1 diabetic patients assisted in a multidisciplinary center presented a better glycemic control, and that the association of the metformin to insulin in type 2 diabetic patients with metabolic syndrome resulted in improvement of the total cholesterol levels and of the patients' glycemic control.

1 INTRODUÇÃO

O Diabetes Melito (DM) é uma das doenças crônicas mais prevalentes na atualidade. De acordo com estimativas da Organização Mundial de Saúde (1), em 1997 existiam 142,5 milhões de portadores de DM no planeta (36,8% nos países desenvolvidos e 63,2% nos países em desenvolvimento), projetando 154,4 milhões para o ano 2000, e 299,9 milhões de pessoas afetadas para 2025 (76% em países em desenvolvimento). Há uma tendência da prevalência aumentar devido ao alargamento da longevidade e às mudanças de hábitos atribuídas à crescente urbanização, inclusive a obesidade.

No Brasil, o impacto do DM na saúde pública, de acordo com dados do Ministério da Saúde, revela que o DM como diagnóstico primário de internação hospitalar aparece como a sexta causa mais freqüente e contribui de forma significativa (30 a 50%) para outras causas, como cardiopatia isquêmica, insuficiência cardíaca, acidente vascular cerebral e hipertensão arterial. Além disso 30% dos pacientes internados em Unidades Coronarianas com dor precordial são diabéticos. É sabido ainda que o DM é a principal causa de cegueira adquirida e de amputações não traumáticas de membros inferiores, e que cerca de 26% dos pacientes que ingressam em programas de diálise são diabéticos (2).

Dados da Fundação Nacional de Saúde (FUNASA) enfatizam que, para o diabetes melito do tipo 1 (DM1), não se dispõe de medidas que previnam sua incidência. Para o diabetes tipo 2 metade dos casos novos poderia ser prevenido evitando-se o excesso de peso, e outros 30% com combate ao sedentarismo; nos diabéticos o controle da pressão arterial previne 80% dos acidentes vasculares cerebrais, 60% das amputações de membros inferiores, 50% das doenças renais terminais e 40% das doenças coronarianas. Além disso programas educativos podem reduzir pela metade o número de hospitalizações por diabetes (3).

Grandes ensaios clínicos, o de Kumamoto (4), o DCCT (*Diabetes Control and Compliations Trial*) (5) e o UKPDS (*United Kingdom Prospective Diabetes Study*) (6) demonstraram a importância de um controle intensivo da glicemia para reduzir as complicações tardias da doença.

O estudo de Kumamoto, publicado antes do UKPDS e realizado no Japão, concluiu que o controle estrito dos níveis plasmáticos de glicose reduziu o risco de nefropatia, neuropatia e retinopatia nos pacientes com DM tipo 2 (4).

Já em relação ao DM tipo 1, o DCCT mostrou que o controle glicêmico intensivo reduziu a retinopatia em 76%, além de reduzir em 54% a progressão para a fase proliferativa. Houve ainda redução de 39% no surgimento de microalbuminúria e 60% no surgimento da neuropatia diabética. O efeito adverso mais importante observado nesse ensaio foi a ocorrência de hipoglicemia, que foi duas a três vezes mais freqüente no grupo que recebeu terapia intensiva com insulina (5).

O UKPDS – o mais longo ensaio clínico já conduzido em indivíduos com diabetes melito do tipo 2 (DM2) – concluiu que para cada um ponto percentual de redução da hemoglobina glicada (A1C) houve redução de 21% nos desfechos relacionados ao DM, bem como na mortalidade relacionada a este, além de redução de 14% na mortalidade geral por todas as causas, redução de 43% nas amputações ou morte por vasculopatia periférica e redução de 37% nas complicações microvasculares (6).

É sabido ainda, segundo dados do UKPDS, que a falência de células beta é progressiva, já que 53% dos pacientes com diabetes do tipo 2 tratados inicialmente com sulfoniluréias passaram a necessitar de insulinoterapia após 6 anos do diagnóstico da doença e esse número aumentou para 80% após 9 anos de diagnóstico, configurando assim a insulinoterapia como uma modalidade terapêutica fundamental também no diabetes do tipo 2 (6).

Frente a esse contexto, várias modalidades de insulinoterapia têm sido propostas, inclusive com inicio precoce nos pacientes com DM2 e associada aos agentes hipoglicemiantes orais.

Apesar disso, os dados da FUNASA (2) indicam que no Brasil a proporção de diabéticos tipo 2 em uso de insulina é da ordem de 8% (contra 25% nos países desenvolvidos), evidenciando ainda uma baixa indicação do uso de insulina no diabetes do tipo 2 no Brasil. Além disso nos pacientes com DM2 é muito comum a associação com a síndrome metabólica, e nesse caso o tratamento deve enfocar outras abordagens visando controlar outros fatores de risco cardiovasculares (3).

O Ministério da Saúde no nosso país vem implementando programas para reduzir o impacto do DM sobre a saúde da população e a economia nacional, porém, devido aos problemas de financiamento do Sistema Único de Saúde (SUS), a distribuição de medicamentos, para o tratamento da hiperglicemia, atualmente se restringe à glibenclamida 5 mg, metformina 850 mg e insulina NPH (humana).

Uma das estratégias adotadas pelo SUS foi a criação de centros de distribuição de insulina, onde os pacientes se consultam com uma equipe multidisciplinar, realizam exames laboratoriais e recebem os frascos de insulina suficientes até a marcação de retorno para a próxima consulta.

A Secretaria de Saúde do município de Juiz de Fora (MG) mantém um desses centros desde 1986 – o Serviço de Controle da Hipertensão, Diabetes e Obesidade (SCHDO), que é um serviço de atendimento secundário localizado no Departamento de Clínica Especializadas. Estima-se que existam cerca de 15.000 diabéticos em Juiz de Fora, para uma população de 456.796 habitantes (Censo 2000, http://www.ibge.gov.br).

O SCHDO é um centro de referência para pacientes hipertensos com complicações e diabéticos usuários de insulina, que vão encaminhados dos ambulatórios de endocrinologia e cardiologia da região.

Os pacientes inscritos contam com o atendimento de uma equipe multi-profissional composta por 4 endocrinologistas, 5 cardiologistas, 3 clínicos gerais, 2 nefrologistas, 2 oftalmologistas, 1 cirurgião especializado em cirurgia bariátrica e 1 enfermeira com treinamento em educação para diabéticos – esta fornece informações sobre uso da insulina, alimentação, hipoglicemias, cuidados com os pés, dentre outras orientações. O serviço conta ainda com 2 auxiliares operacionais de serviços, 1 auxiliar administrativo e 1 digitador.

As consultas mensais são realizadas pelos endocrinologistas. Se necessário os pacientes são novamente encaminhados à enfermeira para reforço das orientações sobre os cuidados gerais. Semanalmente ocorrem reuniões de grupos de diabéticos, supervisionadas pela equipe do serviço, para discussões de temas de interesse dos pacientes, como nutrição, incentivo a atividades físicas, intercorrências e cuidados com os pés. O Serviço dispensa por mês cerca de 4.000 frascos de insulina NPH, 220.000 comprimidos de glibenclamida (5 mg) e 100.000 de metformina (850 mg), além de 425.000 comprimidos de captopril (25 mg), 375.000 de propranolol (40 mg) e 400.000 de hidroclorotiazida (25 mg).

Através da base de dados dos pacientes atendidos no SCHDO realizamos dois estudos.

No primeiro trabalho o objetivo foi avaliar o controle glicêmico de uma coorte de pacientes adultos com DM1 avaliando o impacto da assistência multidisciplinar no controle glicêmico.

O objetivo do segundo trabalho foi comparar um grupo de DM2, portadores de síndrome metabólica, usuários de insulina, antes e 6 meses após a introdução da metformina como tratamento combinado, e avaliar o impacto dessa associação no controle glicêmico, pressão arterial e perfil lipídico.

Os protocolos dos estudos foram aprovados pela Secretaria Municipal de Saúde de Juiz de Fora e pelo Comitê de Ética em Pesquisa da UNIFESP (projeto nº 0783/03).

Alguns resultados preliminares desses estudos foram apresentados no 14º Congresso Brasileiro de Diabetes (Goiânia), na forma dois pôsteres (nº 194 e 195) em 28 de novembro de 2003.

2 PRIMEIRO ARTIGO

TITLE:

GLYCEMIC CONTROL IN ADULT TYPE 1 DIABETES PATIENTS FROM A BRAZILIAN COUNTRY CITY: COMPARISON BETWEEN A MULTIDISCIPLINARY AND A ROUTINE ENDOCRINOLOGICAL APPROACH

AUTHORS:
Carlos Alberto Mourão-Júnior (1,2)
João Roberto de Sá (1)
Olívia Maria Silveira Guedes (2)
Sérgio Atala Dib (1)

INSTITUTIONS:
1. Disciplina de Endocrinologia, Universidade Federal de São Paulo, São Paulo, SP, Brasil.
2. Departamento de Fisiologia, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brasil.

CORRESPONDING AUTHOR:
Carlos Alberto Mourão Júnior
Rua General Mário Xavier, 64
36033-170, Juiz de Fora - MG
Brazil
Phone: +55-32-3236-3948
Fax: +55-32-3215-3130
E-mail: mouraojr@terra.com.br

RUNNING TITLE:
ADULT TYPE 1 DIABETES GLYCEMIC CONTROL

ABSTRACT

Objective: To evaluate the metabolic control of a cohort of adult type 1 diabetes mellitus (T1DM) patients, assisted in a public Diabetes Center (DC), that follows the rules of a national diabetes society.

Methods: We compared the metabolic control and the characteristics of 175 T1DM patients attended by a multidisciplinary team in a DC (test group) with 30 patients assisted only by endocrinologists at a public endocrinology outpatient center (control group) along one year.

Results: The test group presented a larger proportion of well-controlled patients (p= 0.002). The proportions (test group X control group) were the following: 51.4% X 16.7% in the subgroup with A1C < 7%; 21.7% X 36.7% in the subgroup with A1C between 7.1% and 8.0%; and 26.9% X 46.7% in the subgroup with A1C > 8%. The patients assisted in the DC presented a likelihood 4.38 times higher of reaching levels of A1C up to 7%.

Conclusions: This study shows the effectiveness of a DC and emphasizes the importance of education, adherence and multidisciplinarity as cornerstones of the treatment, showing that in developing countries it is possible to treat the T1DM with satisfactory results.

KEYWORDS: Diabetes Mellitus, Type 1 - Insulin - Health Services - Patient Education - Brazil

RESUMO

Objetivo: Avaliar o controle metabólico de uma coorte de pacientes adultos com diabetes do tipo 1 atendidos em um Centro de Diabetes (CD) que segue as normas da Sociedade Brasileira de Diabetes.

Métodos: Foram comparados o controle glicêmico e as características de 175 diabéticos do tipo 1 atendidos por uma equipe multidisciplinar em um CD (grupo teste) com 30 pacientes assistidos em um ambulatório de endocrinologia geral (grupo controle) durante um ano.

Resultados: O grupo teste apresentou uma maior proporção de pacientes bem controlados (p= 0.002). As proporções (grupo teste X grupo controle) foram: 51,4% X 16,7% no subgrupo com A1C < 7%; 21,7% X 36,7% no subgrupo com A1C entre 7,1% e 8,0%; e 26,9% X 46,7% no subgrupo com A1C > 8%. Os pacientes atendidos no CD apresentaram probabilidade 4,38 vezes maior de atingir níveis de A1C até 7%.

Conclusão: O estudo mostra a efetividade do CD e enfatiza a importância da educação, aderência e da multidisciplinaridade como pedras angulares do tratamento, mostrando ser possível tratar o diabetes do tipo 1 nos países em desenvolvimento com resultados satisfatórios.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) corresponds to approximately 10% of all the cases of diabetes and affects between 10 and 20 million individuals worldwide (1). In about 40% of the cases, T1DM appears during the adult age, which begins, in general, less dramatically and eventually can be confused with type 2 diabetes in lean patients (2).

The prevalence of T1DM varies among the studied areas (3) and according to the International Diabetes Federation (IDF) data, this disease is present in approximately 0.11% of the general population of South American countries (4).

Nowadays, it is well established that a great percentage of primary and secondary prevention of chronic diabetes complications can be achieved with a good glycemic control - levels of glycated hemoglobin (A1C) up to 7% - as much in T1DM (5) as in type 2 diabetes mellitus (T2DM) (6), resulting in a reduction of its morbi-mortality and costs (7-9). There are studies showing that in T1DM a significant increase of the prevalence of microangiopathic complications occur when A1C levels are higher than 8%, suggesting such level to be the maximum accepted limit (10-12).

In developing countries, although DM represents a serious public health concern, strict glycemic control is difficult to achieve, owing to financial constraints, cultural obstacles, and lack of adequate infrastructure underlying public services. However, it is known that even in developed countries (13) the goal of reaching an ideal glycemic control is still a great challenge.

In Brazil, the Ministry of Health has been implementing programs to reduce DM impact on the population’s health and the national budget. One of the strategies adopted was to stimulate and to implement the creation of Diabetes Centers (DC) where patients are accepted to be cared for by a multidisciplinary team and receive enough insulin vials until the next consultation. Conversely, the continuous supply of insulin is still a critical point in many developing countries (14).

Such Brazilian Diabetes Society guidelines began to be implemented more than a decade ago, but so far, its impact on the glycemic control of DM patients has not been evaluated. Considering that the adult's T1DM, in spite of being characterized for an insulinopenic state (as in T1DM in the youth), has a more stable behavior (2), and taking into account the complexity of the T2DM treatment (the approach to insulin secretion alteration, insulin resistance, arterial hypertension and dyslipidemia that frequently occur in those patients), we supposed that T1DM in the adult would be a good model for an initial evaluation of the impact of a DC on the patients' glycemic control.

So, the objective of this study was to evaluate the glycemic control of a cohort of adult T1DM patients, treated in a DC of a medium-sized city (Juiz de Fora, Brazil), which follows the recommendations of the Brazilian Diabetes Society, during a one-year period (2003).

MATERIAL AND METHODS

Type 1 Diabetes Mellitus population studied

According to the Brazilian Diabetes Society calculation method it is estimated that there are about 7,632 diagnosed diabetics in Juiz de Fora (approximately 763 Type 1 and 6,869 Type 2) out of a population of 439,716 inhabitants (15).

Description of the outpatient centers

The DC of the Public Health Office of Juiz de Fora has a waiting room, five medical offices, a meeting's room with audiovisual system, an insulin storage room, and offices for a social assistant, a nutritionist and a head nurse/diabetes educator. In addition, there is a pre-appointment's room where the nurse checks patient's body weight, height, blood pressure, abdominal circumference and capillary blood glucose. After the doctor's appointment, the patient receives the insulin vials with a kit for application and the next consultation is scheduled.

The DC patients benefit from the services of a multidisciplinary team comprised of five endocrinologists, a nutritionist, a social assistant, three nurses, two administrative

auxiliaries, and a head nurse certified by the Ministry of Health in diabetes education. When the patient is admitted to DC or whenever a doctor detects some situation that jeopardizes the treatment compliance, the head nurse supplies information to the patient about insulin use, diet, hypoglycemia, foot care and lifestyle. The patients attend bimonthly meetings with all the DC board, in groups of up to 10 patients, where the education strategies are focused using audiovisual methods and discussion groups about nutrition, exercise regimens and foot care, among other topics. The consultations with each member of the DC board last about 60 minutes.

The DC distributes about 4,000 NPH insulin vials a month. At the DC, a great emphasis is placed upon education and the necessity of bimonthly appointment, which is a condition to the patient still receive continuous free insulin.

Juiz de Fora City has also a public general endocrinology center (EC) where, unlike the DC, any kind of endocrinopathy is treated. At the EC only endocrinologists attend the patients without a multidisciplinary approach.

Due to the fact that at both the DC and the EC only NPH insulin is available, all patients are treated with 1 or 2 daily applications of this kind of insulin (fasting and bedtime). The DC and the EC do not offer dipsticks for self-management (capillary glycemia or glycosuria) and the patients' metabolic control is assessed according to A1C and fasting blood glucose (FBG) levels.

Patients

One hundred and seventy five patient records of adult T1DM patients who have received the whole multidisciplinary support available in the DC were analyzed (test group). The records of 30 adult T1DM patients in attendance at the EC were took as a control group. T1DM was classified as the patients for whom the use of insulin was necessary since the onset of the symptoms in order to normalize the glycemic levels, in agreement with the World Health Organization criteria (16).

Patients with T1DM were eligible for inclusion if they were aged equal or above 20 years old at diagnosis and had at least six consultations at the DC in 2003. The patients from the EC have attended up to three consultations during the same period. None of the studied patients had clinical signs of chronic complications. The local ethics committee approved the study.

Methods

The annual (2003) average of the A1C (high performance liquid chromatography, normal value up to 6%) and fasting plasma glucose - FPG - (enzymatic colorimetric method, normal value: 70 to 100 mg/dl = 3.9 to 5.6 mmol/l) were calculated for each patient.

Aiming to assess glycemic control, all patients in our study were divided in three subgroups according to the A1C value: subgroup A (A1C up to 7%), subgroup B (A1C between 7.1 and 8%) and subgroup C (A1C higher than 8%).

The age and patient's gender were analyzed along with DM duration in years, age at the diabetes onset, mean body mass index (BMI) in kg/m^2, daily mean NPH insulin dose in U/kg/day, number of daily insulin applications, patient compliance and acute complications from the database.

In the present study, it was considered as a dietary indiscretion the reported consumption of food with sucrose at least three times a week (17), without including the use of sweets consumed during hypoglycemic episodes. It was considered as a drug misuse any omission in the insulin use reported by the patient (18).

To evaluate the occurrence of acute complications, only hypoglycemic episodes in which the patient reported the classic symptoms followed by an improvement after the ingestion of sweets were computed, having been considered as serious the hypoglycemia that needed the help of others, or with loss of consciousness (19). The ketoacidosis episodes were computed after being confirmed by the hospital discharge summary.

In order to compare the glycemic control between the test (DC) and control (EC) groups the patients' proportions were considered, in both groups, according to the three subgroups of A1C.

Statistical analysis

Continuous variables are expressed as mean ± SD (standard deviation). The categorical variables are expressed as proportions. The comparison of means among the three subgroups was analyzed through the one-way ANOVA, the differences between two means through the Student's t-test (double tail) and the differences among proportions through the chi-square or Fisher's exact test. A logistic binary regression was performed in the whole sample (205 patients) in order to quantify the association between the treatment center (DC or EC) and the glycemic control (outcome), considering other variables that could affect the A1C levels. A p value less than 5% was considered statistically significant. The statistical package Minitab version 14.0 was used to analyze the data.

RESULTS

Description of the test (DC) and control (EC) groups

The test and the control groups were similar to each other in relation to age, gender, time of DM diagnosis, age at clinical picture onset, BMI, number of daily applications of insulin, mean daily dose of insulin, proportion of reports of insulin misuse, and hypoglycemia and ketoacidosis episodes. In the control group, there were more reports of dietary indiscretions and the daily amount of NPH insulin used was greater. The means of the A1C and FPG were lower in the test group, without any overlap between the 99% confidence intervals. These results are summarized in Table 1. The patients' proportion with A1C > 7% that took two applications was greater than those who took just one application in both the test group ($p= 0.039$) and the control group ($p= 0.041$), as verified by the Fisher's exact test.

Analysis of the test group (DC) according to A1C values

The three subgroups (A, B and C) of the test group were similar to each other regarding age, gender, time of DM diagnosis, age of DM onset, mean daily dose of NPH insulin, BMI, number of reports of dietary indiscretions and drug misuse, and number of hypoglycemia reports. In the subgroups with A1C > 7% (B and C) the patients' proportion that took 2 daily applications of NPH insulin was greater. The only three ketoacidosis reports in the test group occurred in the subgroup B. The mean values of A1C were the following: 6.0 ± 0.67% in the subgroup A, 7.51 ± 0.3% in the subgroup B and 9.6 ± 1.15% in the subgroup C. The results are showed in Table 2.

Comparison of glycemic control (DC X EC)

Comparing the test group with the control group, the former presented a higher proportion of well-controlled patients (χ^2 = 12.45, df = 2, p= 0.002). The proportions (test group X control group) were the following: 51.4% X 16.7% in subgroup A (A1C < 7%), 21.7% X 36.7% in subgroup B (A1C between 7.1% and 8.0%) and 26.9% X 46.7% in subgroup C (A1C > 8%), as illustrated in Figure1.

Impact of the DC approach

The logistic regression analysis performed had as a dependent binary variable the groups with A1C up to 7% and A1C > 7%. The numeric independent variables were the patients' age, time of DM diagnosis, mean insulin daily dose and number of daily insulin applications. The independent binary variable was the treatment center (DC X EC). The results showed that age (p= 0.307), time from DM diagnosis (p= 0.801), daily insulin dose (p= 0.284) and number of applications (p= 0.082) did not present significant influence on the tested outcome (A1C up to 7% X A1C > 7%). However, the center where the patient was assisted was the factor of decisive influence (p= 0.006, positive coefficient of 1.48), showing that patients assisted at the DC presented a likelihood 4.38 times higher of presenting levels of A1C up to 7% (OR = 4.38, 95% CI = 1.53 to 12.57, p= 0.006). All the assumptions of the logistic regression analysis were verified (Log-Likelihood test: p < 0.001) and the model's

goodness-of-fit was confirmed by the tests of Pearson (p= 0.415) and Hosmer-Lemeshow (p= 0.108). The association measures were solid (Goodman-Kruskal Gamma coefficient = 0.34) (20).

DISCUSSION

According to the estimated T1DM prevalence and the population of the city studied our work included about 23% of them. There are patients that do not adapt to the DC regimen, such as consultation periodicity and participation in the weekly groups of DM education.

In the period of the study (1 year), there was a significant proportion of patients with desirable metabolic control in the test group, despite the fact that all patients (due to a limitation of basic resources, like fast-acting insulin and dipsticks for self-management supply) were treated with conventional insulin therapy (one or two daily applications of NPH). However, similar reports exist both in national and international literature (21,22). As our sample was composed by adult T1DM patients, perhaps with a larger endogenous insulin reserve (23), glycemic control may have been facilitated. Data from a Belgian study of children and adolescents using up to two daily insulin doses, showed that 62% of the studied group reached a good metabolic control (22), as well as demonstrated by another Brazilian study (21).

The frequency of DC consultations (which was bimonthly in our study), specialists care and a structured DM education service might have collaborated in obtaining results with the use of conventional insulin therapy (22,24).

This approach with one or two daily insulin applications, for several reasons, is still frequently used in several countries in the treatment of T1DM. A multicentric study (13) involving 18 countries showed that 60% of the T1DM patients were in the regimen of two daily insulin doses and 34% of them presented good glycemic control - an inferior percentage in comparison to our group and in the studies previously mentioned (21,22), perhaps because the analyzed patients had not been assisted in structured DCs.

Anyway, regardless of the therapeutic modality utilized, the percentage of patients that do not reach the ideal metabolic control worldwide is still high even with intensive insulin therapy, including developed countries (10,24,25).

It is known that T1DM is a disease that requires great commitment by patients to reach the desired goals. The patients' compliance is difficult to achieve, perhaps providing an explanation to difficulty to get the desired metabolic control, as mentioned above.

It is plausible to presume that the multidisciplinary team's effort for improving the patients' adherence explain the relatively high amount of patients with better metabolic control at the DC (26).

In regards to the ideal metabolic control (A1C up to 7%), 51.4% of the patients assisted at the DC reached such goal, versus only 16.7% in the control group. In addition, it was statistically confirmed that the patients assisted at the DC presented a likelihood 4.38 times higher of reaching levels of A1C up to 7%.

The characteristics of the patients studied, such as gender, duration of the disease, age at the onset of the disease, mean dose of insulin used and BMI do not differ from other national (27-29) and international (5) studies. Given a more advanced age of our patients, it is possible that some of them presented LADA, although patients with LADA sometimes do not require insulin at diagnosis (30).

The T1DM diagnosis could not be confirmed with laboratorial methods, since autoantibody measurement was not available where the study was carried out; furthermore nowadays the precise diagnosis of T1DM is far from straightforward (2, 31-34).

In the test group, the patients with worse metabolic control used two insulin applications more frequently than the group with better control. It is probable that the option of changing from one to two applications had been based on this criterion. Although a study accomplished in Belgium demonstrated no difference in the metabolic control of patients using insulin two or four times a day (22).

The number of reports of dietary indiscretions and drug misuse was equivalent in the three studied subgroups of the test group. In the control group, there were more dietary indiscretions, showing fewer adherences of these patients.

There were 43 hypoglycemia reports in our sample without the need of help from others for the patients' recovery. In fact, the studies show that the frequency of serious hypoglycemia is directly related to intensive glycemic control (5,35).

The four episodes of reported ketoacidosis occurred in patients due to omission of insulin use.

Anyway, 26.9% of the patients of the test group maintained levels of A1C above 8%. Besides the possibilities discussed above, it is probable that the simultaneous use of fast-acting insulin and self-management could improve this situation. Accordingly to Almeida et al (29), in Latin America only Brazil, Cuba and Costa Rica distribute insulin gratuitously, and only Costa Rica, among 12 studied countries, supplies necessary material for the patients' self-management.

Several limitations of our study must be considered concerning the generalization of our results. We studied adult T1DM with a probably better insulin reserve, our patients were very adherent to the proceedings of the DC and we carried out a historical cohort analysis (in the future prospective clinical trials may assess our results).

Besides, in our study it is possible that mild hypoglycemia episodes may have occurred and this fact could be related to the found A1C levels, although in the control group the mean dose of NPH insulin was larger. We could not evaluate this fact due to the lack of self-management of the capillary glycemia.

Probably the chief fact that could explain our relatively good results concerning the glycemic control is that all the patients were completely adherent to the DC rules, furthermore other studies showed that when the therapeutic strategies are very complex it can impair the patients’ adherence (36,37).

To sum up, this study demonstrated that patients attended by a structured multidisciplinary team, with emphasis on the patient's education with good adherence, continuous supply of insulin, were capable of reaching satisfactory results even without resources for self-management of the glycemia and using only NPH insulin, evidencing that in developing countries it is possible to improve the patients' glycemic control even when intensive insulin therapy is not available.

REFERENCES

1. Halimi S, Benhamou PY. Diabetes, a worldwide disease. **Presse Med 2004**;33 Spec No:Sp37-40.

2. Sabbah E, Savola K, Ebeling T, Kulmala P, Vahasalo P, Ilonen J, et al. Genetic, autoimmune, and clinical characteristics of childhood- and adult-onset type 1 diabetes. **Diabetes Care 2000**;23(9):1326-1332.

3. Karvonen M, Tuomilehto J, Libman I, LaPorte R. A review of the recent epidemiological data on the worldwide incidence of Type 1 (insulin-dependent) diabetes mellitus. **Diabetologia 1993**;36:883-92.

4. Malerbi D, Franco L. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69 yr. The Brazilian Cooperative Group on the Study of Diabetes Prevalence. **Diabetes Care 1992**;15(11):1509-16.

5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. **N Engl J Med 1993**;329(14):977-86.

6. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). **Lancet 1998**;352(9131):837-53.

7. The Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. **Jama 1996**;276(17):1409-15.
8.Leichter SB. The business of insulin: a relationship between innovation and economics. **Clin Diabetes 2003**;21(1):40-42.

9.American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. **Diabetes Care 2003**;26(3):917-32.

10. Chase HP. Glycemic control in prepubertal years. **Diabetes Care 2003**;26(4):1304-05.

11. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. **N Engl J Med 1995**;332(19):1251-55.

12. Warram JH, Manson JE, Krolewski AS. Glycosylated hemoglobin and the risk of retinopathy in insulin-dependent diabetes mellitus. **N Engl J Med 1995**;332(19):1305-06.

13. Mortensen HB, Hougaard P. Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 countries. **Diabetes Care 1997**;20(5):714-20.

14. Yudkin JS. Insulin for the world's poorest countries. **Lancet 2000**;355(9207):919-21.

15. Sociedade Brasileira de Diabetes. Proposta básica para a assistência ao diabético no município. Available from: www.diabetes.org.br/centros/como.php, consulted in 2005.

16. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. 1999.

17. Ney D, Stubblefield N, Fischer C. A tool for assessing compliance with a diet for diabetes. **J Am Diet Assoc 1983**;82(3):287-90.

18. Bryden KS, Neil A, Mayou RA, Peveler RC, Fairburn CG, Dunger DB. Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. **Diabetes Care 1999**;22(12):1956-60.

19. McCrimmon RJ, Frier BM. Hypoglycaemia, the most feared complication of insulin therapy. **Diabete Metab 1994**;20:503-12.

20. Hosmer DW, Hjort NL. Goodness-of-fit processes for logistic regression: simulation results. **Stat Med 2002**;21(18):2723-38.

21. Silva Júnior GR, Fucks AG, Cunha EF, Clemente ELS, Gomes MB. Inter-relação de variáveis demográficas, terapêutica insulínica e controle glicêmico em pacientes com diabetes mellitus do tipo 1 atendidos em um hospital universitário. **Arq Bras Endocrinol Metabol 1999**;43(2):114-20.

22. Dorchy H, Roggemans M, Willems D. Glycated hemoglobin and related factors in diabetic children and adolescents under 18 years of age:a Belgian experience. **Diabetes Care 1997**;20(1):2-6.

23. Linn T, Mann M, Boedeker RH, Bretzel RG. Why is a new trial required to define the role of insulin reserve in newly diagnosed adult type 1 diabetes? **Exp Clin Endocrinol Diabetes 2003**;111(6):319-21.

24. Tabák AG, Tamás G, Zgibor J, Wilson R, Becker D, Kerényi Z, et al. Targets and reality: a comparison of health care indicators in the U.S. (Pittsburgh Epidemiology of Diabtes Study) and Hungary (DiabCare Hungary). **Diabetes Care 2000**;23(9):1284-89.

25. Davidson MB. Quality and the art of diabetes maintenance. Professional section quartely. **News from the American Diabetes Assiciation 1997**;Summer.

26. Rhee MK, Slocum W, Ziemer DC, Culler SD, Cook CB, El-Kebbi IM, et al. Patient adherence improves glycemic control. **Diabetes Educ 2005**;31(2):240-50.

27. Silveira VMF, Menezes AMB, Post CLA, Machado EC. Uma amostra de pacientes com diabetes tipo 1 no sul do Brasil. **Arq Bras Endocrinol Metabol 2001**;45(5):433-40.

28. Fernandes VT, Verreschi IT, Dib SA. Development according to pubertal stage in Brazilian children and adolescents with short-term diabetes. **Braz J Med Biol Res 2001**;34(10):1315-23.

29. Almeida HGG, Campos JJB, Kfouri C, Tanita MT, Dias AE, Souza MM. Perfil de pacientes diabéticos tipo 1: insulinoterapia e automonitorização. **Rev Assoc Med Bras 2002**;48(2):151-55.

30. Pozzilli P, Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (Latent Autoimmune Diabetes of the Adult). **Diabetes Care 2001**;24:1460-67.

31. Hosszufalusi N, Vatay A, Rajczy K, Prohaszka Z, Pozsonyi E, Horvath L, et al. Similar Genetic Features and Different Islet Cell Autoantibody Pattern of Latent Autoimmune Diabetes in Adults (LADA) Compared With Adult-Onset Type 1 Diabetes With Rapid Progression. **Diabetes Care 2003**;26(2):452-457.

32. Aguilera E, Casamitjana R, Ercilla G, Oriola J, Gomis R, Conget I. Adult-Onset Atypical (Type 1) Diabetes: Additional insights and differences with type 1A diabetes in a European Mediterranean population. **Diabetes Care 2004**;27(5):1108-1114.

33. Palmer JP, Hampe CS, Chiu H, Goel A, Brooks-Worrell BM. Is Latent Autoimmune Diabetes in Adults Distinct From Type 1 Diabetes or Just Type 1 Diabetes at an Older Age? **Diabetes 2005**;54(suppl_2):S62-67.

34. Seissler J, de Sonnaville JJ, Morgenthaler NG, Steinbrenner H, Glawe D, Khoo-Morgenthaler UY, et al. Immunological heterogeneity in type I diabetes: presence of distinct autoantibody patterns in patients with acute onset and slowly progressive disease. **Diabetologia 1998**;41(8):891-7.

35. Bott S, Bott U, Berger M, Muhlhauser I. Intensified insulin therapy and the risk of severe hypoglycaemia. **Diabetologia 1997**;40(8):926-32.

36. Cramer JA. A Systematic Review of Adherence With Medications for Diabetes. **Diabetes Care 2004**;27(5):1218-1224.

37. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. **Am J Med 2005**;118 Suppl 5A:27S-34S.

TABLES

Table 1 - Characteristics of patients in the test group and control group after one year.

	Test Group (n = 175)	Control Group (n = 30)	p value
Age (years)	42.4 ± 14.2	42.6 ± 13.2	0.949
Gender (M/F)	83/92	13/17	0.698
Disease duration (years)	12.9 ± 9.2	12.5 ± 8.5	0.812
Age at DM onset (years)	29.4 ± 8.4	30.0 ± 12.0	0.721
FPG (mmol/l)*	9.6 ± 2.5 [9.1 to 10.1]	11.0 ± 1.6 [10.2 to 11.8]	0.003
A1C (%)*	7.28 ± 1.70 [6.94 to 7.61]	8.36 ± 1.07 [7.82 to 8.99]	0.001
NPH mean dose (U/kg/day)*	0.98 ± 0.47	1.23 ± 0.94	0.025
BMI (kg/m^2)	27.3 ±17.1	28.6 ± 4.4	0.679
Number of doses (1 dose/2 doses)	50/125	6/24	0.383
Dietary indiscretions*	42	13	0.043
Drug misuse	24	5	0.776
Hypoglycemic episodes	40	3	0.149
Ketoacidotic episodes	3	1	0.472
Number of consultations	6	up to 3	-

Data are n or mean ± SD. Values between brackets represent the 99% confidence interval.
*p< 5%. To convert mg/dl to mmol/l the used factor was 0.05551.

Table 2 - Characteristics of patients in the test group, according to the A1C interval after one year.

	Subgroup A (n = 90) A1C < 7%	Subgroup B (n = 38) A1C: 7.1% to 8.0%	Subgroup C (n = 47) A1C > 8.0%	p value
Age (years)	41.7 ± 13.7	41.2 ± 14.6	44.6 ± 14.8	0.459
Gender (M/F)	45/45	19/19	19/28	0.532
Disease duration (years)	12.5 ± 8.9	12.6 ± 9.7	14.2 ± 9.4	0.595
Age at DM onset (years)	29.2 ± 8.3	28.6 ± 8.2	30.4 ± 8.9	0.596
NPH mean dose (U/kg/day)	0.95 ± 0.46	1.10 ± 0.42	1.04 ± 0.5	0.211
BMI (kg/m^2)	27.8 ± 23.1	26.0 ± 5.9	27.2 ± 6.4	0.855
Number of doses (1 dose/2 doses)*	32/58	4/34	14/33	0.016
Dietary indiscretions	22	7	13	0.606
Drug misuse	13	8	3	0.142
FPG (mmol/l)*	7.7 ± 1.0	10.0 ± 0.4	13.1 ± 1.7	0.001
Hypoglycemic episodes	23	7	10	0.650
Ketoacidotic episodes*	0	3	0	0.006

Data are n or mean ± SD. *p< 5%.

FIGURE

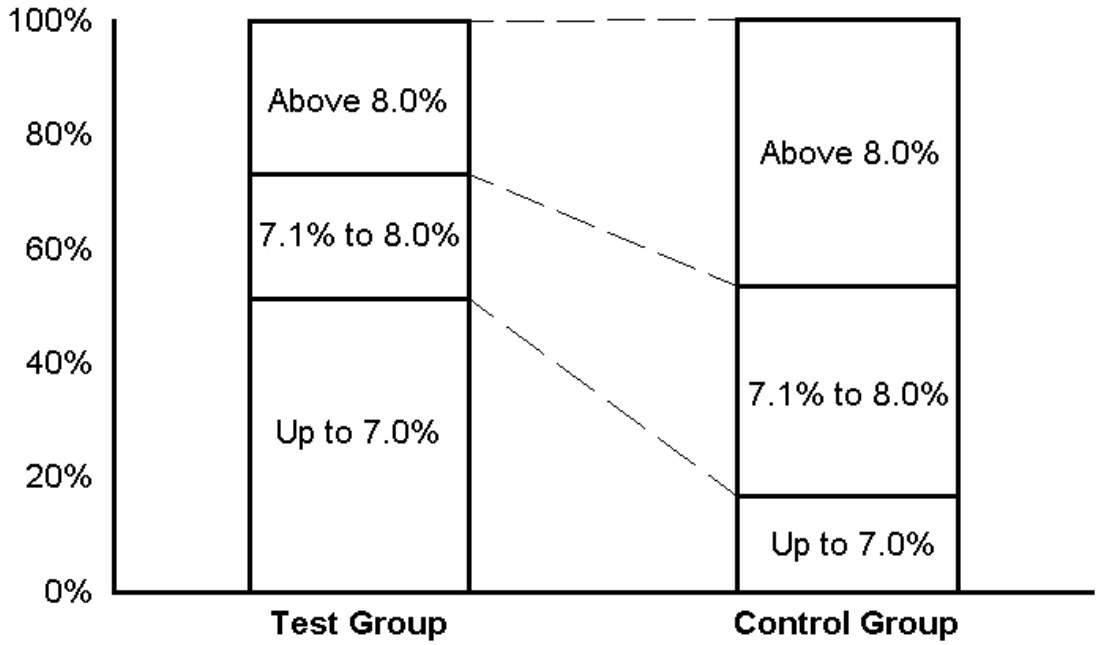

Figure 1 - Patients' proportions according to the A1C level subgroups in the test group (n = 175) and in the control group (n = 30).

3 SEGUNDO ARTIGO

Brazilian Journal of Medical and Biological Research (2006) 39:
ISSN 0100-879X

Effects of metformin on the glycemic control, lipid profile, and arterial blood pressure of type 2 diabetic patients with metabolic syndrome already on insulin

C.A. Mourão-Júnior[1,2], J.R. Sá[1], O.M.S. Guedes[2] and S.A. Dib[1]

[1]Disciplina de Endocrinologia, Universidade Federal de São Paulo, São Paulo, SP, Brasil
[2]Departamento de Fisiologia, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brasil

Correspondence
C.A. Mourão Júnior
Rua General Mário Xavier, 64
36033-170 Juiz de Fora, MG
Brasil
Fax: +55-32-3215-3130
E-mail: mouraojr@terra.com.br

Publication supported by FAPESP.

Received September 12, 2005
Accepted February 13, 2006

Abstract

Fifty-seven type 2 diabetic patients with metabolic syndrome and on insulin were assessed by a paired analysis before and 6 months after addition of metformin as combination therapy to evaluate the impact of the association on glycemic control, blood pressure, and lipid profile. This was a historical cohort study in which the files of type 2 diabetic patients with metabolic syndrome on insulin were reviewed. The body mass index (BMI), waist circumference, lipid profile, A1C level, fasting blood glucose level, daily dose of NPH insulin, systolic blood pressure, and diastolic blood pressure were assessed in each patient before the start of metformin and 6 months after the initiation of combination therapy. Glycemic control significantly improved ($P < 0.001$) after the addition of metformin (1404.4 ± 565.5 mg/day), with 14% of the 57 patients reaching A1C levels up to 7%, and 53% reaching values up to 8%. There was a statistically significant reduction ($P < 0.05$) of total cholesterol (229.0 ± 29.5 to 214.2 ± 25.0 mg/dL), BMI (30.7 ± 5.4 to 29.0 ± 4.0 kg/m^2), waist circumference (124.6 ± 11.7 to 117.3 ± 9.3 cm), and daily necessity of insulin. The reduction of total cholesterol occurred independently of the reductions of A1C (9.65 ± 1.03 to 8.18 ± 1.01%) and BMI and the reduction of BMI and WC did not interfere with the improvement of A1C. In conclusion, our study showed the efficacy of the administration of metformin and insulin simultaneously without negative effects. No changes were detected in HDL-cholesterol or blood pressure.

Key words
- Type 2 diabetes mellitus
- Metabolic syndrome
- Metformin
- Blood pressure
- Cholesterol
- Triglycerides

Introduction

The need for strict glycemic control in order to avoid or postpone the development of late complications in patients with type 2 diabetes mellitus (DM2) has been well established (1). It has been shown that the onset of complications may be related to glycosylated hemoglobin (A1C) levels higher than 7%, a situation that is even more likely if glycemic control is poor, with A1C levels above 8% (2). Although the initial management of DM2 involves lifestyle changes and oral hypoglycemic drugs, a significant num-

ber of patients will need insulin in order to reach satisfactory glycemic control (3). Furthermore, DM2 does not mean glycemic alterations alone since this disease is associated with cardiovascular risk factors such as dyslipidemia, systemic arterial hypertension, and obesity (4). This association is clinically relevant since over 50% of deaths among DM2 patients are due to cardiovascular disease (5).

Treatment of DM2 must include pharmacological agents able to improve not only glycemic levels, but also blood pressure (BP), lipid levels, and body weight, since in approximately 90% of type 2 diabetics hyperglycemia is associated with other cardiovascular factors that constitute the metabolic syndrome.

Several studies (6,7) have demonstrated that, in order to prevent the development and progression of chronic complications of diabetes, a comprehensive approach to all elements of the metabolic syndrome is required. The main feature of the metabolic syndrome, which can be clinically assessed by measurement of the waist circumference (WC) whenever more sophisticated laboratory methods are not available (8), is insulin resistance.

After metformin proved to be effective in reducing insulin resistance (9), several studies were undertaken to assess its effects on total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL-C) levels, and also on BP and body mass index (BMI). However, there is no consensus about its beneficial effects on these parameters (10). Most studies have analyzed independent samples, comparing patients on insulin with patients on combined insulin-metformin therapy (11-13) with no conclusive results.

The objective of the present study was to assess a group of DM2 patients with metabolic syndrome, on insulin, before and 6 months after the introduction of metformin as combined therapy, so as to evaluate the effect of this association on glycemic control, BP, and the lipid profile.

Patients, Material and Methods

Data collection

We undertook a historical cohort study by assessing the medical files of type 2 diabetic patients with metabolic syndrome, on insulin, seen at a public diabetes-dedicated facility in a medium-sized Brazilian city (Juiz de Fora). All patients were followed up bimonthly by a team composed of four endocrinologists, a nutritionist, and a diabetes-trained nurse.

Patient selection

We selected files of patients who had been on twice daily injections of NPH insulin and who had metformin added to their therapy. Any file that showed any dietary indiscretion or drug misuse was not utilized in the study. A dietary indiscretion was defined as the intake of sucrose-containing foods three or more times a week, not considering the use of sweet foods taken during hypoglycemic episodes. A drug misuse was defined as any failure to take the prescribed drugs, as reported by the patient.

To avoid the inclusion of late-onset type 1 DM patients in the sample, we studied only patients with documented control of their disease with oral hypoglycemic drugs alone for at least 5 years before they began insulin treatment, and who showed no evidence of previous episodes of ketoacidosis. All patients followed the same diet, prescribed and monitored by the nutritionist.

The patients were diagnosed as having metabolic syndrome if they fulfilled at least 3 of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP ATP III) criteria (14). Although other criteria exist, as the World Health Organization criteria, the NCEP ATP III was the most widely used classification at present (6).

All patients had type 2 diabetes mellitus (blood glucose >126 mg/dL), high triglycer-

ide levels (>150 mg/dL), and increased WC (women: >88 cm; men: >102 cm). Table 1 shows the patients' characteristics.

A patient on anti-hypertensive or lipid-lowering drugs was only included if there was no change in the dosages of these drugs throughout the study period. Full attendance of scheduled consultations was another inclusion criterion.

Variables studied

BMI, WC, lipid profile (TC, HDL-C, and TG), A1C, fasting blood glucose (FBG), daily dose of NPH insulin, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in each patient before the start of metformin and 6 months after initiation of combined therapy.

Weight measurements were made only once, with a digital scale with a maximum capacity of 180 kg and precision of up to 100 g. The patients were weighed in their underwear after carefully stepping onto the center of the scale.

Height was measured only once, with a 1-mm precision tape measure fixed to the wall, with the zero mark at floor level. The patients were standing, with bare feet kept together, and with heels and occiput touching the tape.

For WC measurement, the patients were standing, with abdomen relaxed, upper limbs falling along the body, and the tape placed horizontally, halfway between the lower margin of the last rib and the iliac crest; the measurements were made with the tape firmly applied to the pelvis but without tissue compression. A flexible 1-mm precision tape measure was used.

Blood pressure was measured three times within a 10-min interval on the left arm, with the patient in the supine position, after a 5-min rest, with a calibrated mercury sphygmomanometer.

TC, HDL-C, TG, and FBG levels were measured by the colorimetric method, with maximum acceptable values of 240 mg/dL (TC), 200 mg/dL (TG), and 110 mg/dL (FBG). The minimum acceptable value for HDL-C was 35 mg/dL. A1C was measured by high-performance liquid chromatography (normal reference for stable A1C in non-diabetic patients is 2.8 to 5.2%, according to the National Glycohemoglobin Standardization Program). All laboratory determinations were performed automatically. The study was approved by the local Ethics Committee and all patients signed written informed consent.

Statistical analysis

The data are reported as means ± SD, percentages (%) or 95% confidence intervals (95% CI). All tests were two-tailed, and the level of significance was set at $P < 5\%$.

In order to compare the means of the study variables before and after the introduction of metformin, a paired *t*-test with 95% CI of the means was used. If the *t*-test showed a difference for any variable studied, Pearson's correlation test was performed to check for possible intervening variables (co-variance) by the analysis of the coefficient of determination (r^2) and r 95% CI. All assumptions for the undertaking of parametric tests were checked and accounted for. The statistical package GraphPad InStat, version 3.06, for Windows (San Diego, CA, USA) was used in the analyses.

Table 1. Characteristics of the cohort.

Demographics	
N	57
Age (years)	58.9 ± 8.0
Duration of diabetes (years)	15.9 ± 5.7
Daily metformin dose (mg)	1404.4 ± 565.5
Sex (male/female)	26/31
Concomitant medication	
Lipid-lowering drugs	18 (31)
Blood pressure-lowering drugs	32 (56)

Data are reported as means ± SD or N (%).

Results

Fifty-seven files met the inclusion criteria and were analyzed in this study.

There was a statistically significant reduction of the daily dose of NPH insulin, of BMI, WC and TC, and TG levels when the values before and 6 months after metformin were compared. Neither BP (SBP or DBP), nor HDL-C suffered any alteration. Table 2 summarizes the comparative measurements.

Glycemic control improved significantly ($P < 0.0001$) after the introduction of metformin, with a reduction of mean FBG and A1C levels (Table 2). Furthermore, 14% of the patients reached A1C levels of up to 7%, 53% had A1C values of up to 8%, and 47% had unsatisfactory glycemic control. Before metformin introduction, all patients had A1C >8%. Correlation tests showed that TC reduction was independent of reductions in A1C, WC, and BMI. Reduction of BMI and WC also did not interfere with glycemic control. However, a slight correlation was seen between reduction of TG and BMI ($r^2 = 12.5\%$), and TG and WC ($r^2 = 8\%$), suggesting a certain degree of co-variance. The correlations calculated can be analyzed by the determination coefficients and 95% CI shown in Table 3.

None of the files showed reports of severe hypoglycemia, i.e., a situation needing somebody's help. Although there were 16 reports (28% of the sample) of transient, mild gastrointestinal upset (dyspepsia) at the beginning of metformin use, there was no necessity of dose reduction or withdrawal.

Anti-hypertensive drugs were hydrochlorothiazide, propranolol, and captopril. Patients with dyslipidemia used lovastatin and gemfibrozil. These drugs probably did not interfere with the results, as there was no alteration in dose or type of drug used throughout the study period.

Table 2. Comparison of clinical and laboratory variables before and 6 months after the introduction of metformin.

	Before	After	95% CI
A1C (%)	9.65 ± 1.03	8.18 ± 1.01*	1.09 to 1.86
FBG (mg/dL)	215.3 ± 28.0	167.2 ± 27.3*	37.5 to 58.6
Daily insulin dose (IU kg^{-1} day^{-1})	0.83 ± 0.39	0.69 ± 0.36*	0.02 to 0.26
BMI (kg/m^2)	30.7 ± 5.4	29.0 ± 4.0*	0.1 to 3.3
Waist circumference (cm)	124.6 ± 11.7	117.3 ± 9.3*	3.6 to 10.9
Total cholesterol (mg/dL)	229.0 ± 29.5	214.2 ± 25.0*	4.9 to 24.7
HDL cholesterol (mg/dL)	37.5 ± 8.4	38.0 ± 6.3	-3.4 to 2.3
Triglycerides (mg/dL)	236.2 ± 40.2	218.5 ± 42.4*	1.5 to 34.0
Systolic blood pressure (mmHg)	158 ± 25	156 ± 18	-7 to 11
Diastolic blood pressure (mmHg)	92 ± 11	90 ± 14	-3 to 6

Data are reported as means ± SD. A1C = glycohemoglobin level; FBG = fasting blood glucose. *P < 0.05 compared to before metformin treatment (Student *t*-test).

Table 3. Pearson's correlation test applied to pairs of variables.

Variables	P value	r	95% CI	r^2
TC and A1C	0.597	-0.072	-0.326 to 0.193	0.5%
TC and BMI	0.237	0.159	-0.106 to 0.403	2.5%
TC and WC	0.555	0.079	-0.185 to 0.334	0.6%
TG and A1C	0.605	0.070	-0.194 to 0.325	0.5%
TG and BMI*	0.007	0.354	0.102 to 0.562	12.5%
TG and WC*	0.033	0.282	0.023 to 0.505	8%
A1C and BMI	0.056	0.254	-0.007 to 0.483	6.4%
A1C and WC	0.926	0.012	-0.272 to 0.249	0.01%

TC = total cholesterol; A1C = glycohemoglobin level; BMI = body mass index; WC = waist circumference; TG = triglycerides; r = correlation coefficient; r^2 = coefficient of determination. *P < 0.05.

Discussion

Glycemic control

The present study showed that the addition of metformin to a scheme of NPH insulin administered twice daily improved glycemic control of type 2 diabetic patients with the metabolic syndrome after 6 months, regardless of BMI reduction, as already shown in other studies (11,12). Although one study showed that metformin can lead to WC reduction (15), the improvement of A1C levels in our sample was independent of WC reduction, indicating that metformin improves sensitivity to the action of insulin by mechanisms already described, such as inhibition of hepatic gluconeogenesis (16). Al-

though over half the patients reached A1C levels below 8%, only 14% reached ideal metabolic control (A1C up to 7%), and 47% kept their A1C above 8%. More intensive insulin therapy with fast-acting insulins and self-monitoring might have led to better results (17). The mean FBG and A1C values of our patients were similar to those reported in other studies (11-13), although most studies did not report the percentage of patients who reached the established cut-off points for A1C. Such information would have shed light on the extent of glycemic control reached at other centers, since the mean value is sensitive to extreme values.

Lipid profile

The literature shows discrepant results about the influence of metformin on lipid profile (10). Some studies, in agreement with ours, reported reduction only in TC levels (18,19), while others reported reduction of TC and TG with an increase of HDL-C (20,21). Still other studies showed no changes in lipid profile (22,23). Another investigation showed an association of metformin with an improvement in the lipid profile even in non-diabetic patients (24). New studies are needed to clarify this issue, since TG and HDL-C are very important parameters for the evaluation of metabolic syndrome.

A possible reason for these discrepant results may be that the clinical studies cited above analyzed data from independent samples. In our study, this problem was avoided by paired data analysis, in which each patient was his own control, thereby increasing the power of the statistical analysis.

A recent meta-analysis (10) covering 41 studies on the effects of metformin on BP and lipid profile showed that only TC reduction was significant. Our results are in agreement with these findings and show that this fact was independent of BMI and WC reduction. Since the TG reduction found in the present study underwent interference from BMI and WC (intervening variables), we cannot conclude that metformin had a direct and isolated effect on TG levels.

Other parameters

The fact that metformin did not reduce BP in our sample agrees with other studies (10,22,23,25), although there are reports of SBP and DBP reduction with this drug (26,27). A possible explanation for this discrepancy may be the fact that not all patients who lose weight experience reductions in their plasma renin and aldosterone levels (28,29). However, metformin is known to positively affect other parameters which influence the development of cardiovascular disease, regardless of any effect on BP (30, 31). Our results agree with the literature regarding the effect of metformin on BMI reduction (9,12,13), reduction of daily insulin dose (9,12,13), biguanide-related side-effects (21,24), and reduction of WC, which is a cornerstone for the diagnosis of metabolic syndrome and may play the role of a co-variate when other parameters are analyzed (18,32).

In conclusion, our study showed the efficacy of the administration of metformin and insulin simultaneously without negative effects and no changes were detected in HDL-cholesterol or blood pressure.

References

1. Stratton IM, Adler AI, Neil HA et al. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *British Medical Journal*, 321: 405-412.

2. Krolewski AS, Laffel LM, Krolewski M et al. (1995). Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *New England Journal of Medicine*, 332: 1251-1255.

3. Turner RC, Cull CA, Frighi V et al. (1999). Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *Journal of the American Medical Association*, 281: 2005-2012.
4. Reaven GM (1988). Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*, 37: 1595-1607.
5. Gu K, Cowie CC & Harris MI (1998). Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care*, 21: 1138-1145.
6. van der Kallen CJ, Voors-Pette C & de Bruin TW (2004). Abdominal obesity and expression of familial combined hyperlipidemia. *Obesity Research*, 12: 2054-2061.
7. Lorenzo C, Okoloise M, Williams K et al. (2003). The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care*, 26: 3153-3159.
8. Poirier P, Lemieux I, Mauriege P et al. (2005). Impact of waist circumference on the relationship between blood pressure and insulin: the Quebec Health Survey. *Hypertension*, 45: 363-367.
9. Despres JP (2003). Potential contribution of metformin to the management of cardiovascular disease risk in patients with abdominal obesity, the metabolic syndrome and type 2 diabetes. *Diabetes and Metabolism*, 29: 6S53-6S61.
10. Wulffele MG, Kooy A, de Zeeuw D et al. (2004). The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *Journal of Internal Medicine*, 256: 1-14.
11. Jaber LA, Nowak SN & Slaughter RR (2002). Insulin-metformin combination therapy in obese patients with type 2 diabetes. *Journal of Clinical Pharmacology*, 42: 89-94.
12. Strowig SM, Viles-Santa ML & Raskin P (2002). Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes. *Diabetes Care*, 25: 1691-1698.
13. Wulffele MG, Kooy A, Lehert P et al. (2002). Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care*, 25: 2133-2140.
14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association*, 285: 2486-2497.
15. Pasquali R, Gambineri A, Biscotti D et al. (2000). Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism*, 85: 2767-2774.
16. Kirpichnikov D, McFarlane SI & Sowers JR (2002). Metformin: an update. *Annals of Internal Medicine*, 137: 25-33.
17. DeWitt DE & Dugdale DC (2003). Using new insulin strategies in the outpatient treatment of diabetes: clinical applications. *Journal of the American Medical Association*, 289: 2265-2269.
18. Ginsberg H, Plutzky J & Sobel BE (1999). A review of metabolic and cardiovascular effects of oral antidiabetic agents: beyond glucose-level lowering. *Journal of Cardiovascular Risk*, 6: 337-346.
19. Grant PJ (1996). The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. *Diabetes Care*, 19: 64-66.
20. Yki-Jarvinen H, Ryysy L, Nikkila K et al. (1999). Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Annals of Internal Medicine*, 130: 389-396.
21. Robinson AC, Burke J, Robinson S et al. (1998). The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control. *Diabetes Care*, 21: 701-705.
22. Groop L, Widen E, Franssila-Kallunki A et al. (1989). Different effects of insulin and oral antidiabetic agents on glucose and energy metabolism in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*, 32: 599-605.
23. Rains SG, Wilson GA, Richmond W et al. (1988). The effect of glibenclamide and metformin on serum lipoproteins in type 2 diabetes. *Diabetic Medicine*, 5: 653-658.
24. DeFronzo RA & Goodman AM (1995). Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *New England Journal of Medicine*, 333: 541-549.
25. Nagi DK & Yudkin JS (1993). Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes Care*, 16: 621-629.
26. Giugliano D, Quatraro A, Consoli G et al. (1993). Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. *European Journal of Clinical Pharmacology*, 44: 107-112.
27. Landin K, Tengborn L & Smith U (1991). Treating insulin resistance in hypertension with metformin reduces both blood pressure and metabolic risk factors. *Journal of Internal Medicine*, 229: 181-187.
28. Manrique C, Lastra G, Whaley-Connell A et al. (2005). Hypertension and the cardiometabolic syndrome. *Journal of Clinical Hypertension*, 7: 471-476.
29. Tuck ML, Sowers J, Dornfeld L et al. (1981). The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. *New England Journal of Medicine*, 304: 930-933.
30. Katakami N, Yamasaki Y, Hayaishi-Okano R et al. (2004). Metformin or gliclazide, rather than glibenclamide, attenuate progression of carotid intima-media thickness in subjects with type 2 diabetes. *Diabetologia*, 47: 1906-1913.
31. Schafers RF (2003). Do effects on blood pressure contribute to improved clinical outcomes with metformin? *Diabetes and Metabolism*, 29: 6S62-6S70.
32. Meenakumari KJ, Agarwal S, Krishna A et al. (2004). Effects of metformin treatment on luteal phase progesterone concentration in polycystic ovary syndrome. *Brazilian Journal of Medical and Biological Research*, 37: 1637-1644.

4 CONSIDERAÇÕES FINAIS

4.1 Primeiro artigo

- O percentual relativamente alto de pacientes controlados com terapia convencional pode ser atribuído a fatores como freqüência de consultas (que no caso de nosso estudo foi bimestral), atendimento por especialistas e um serviço de educação em diabetes estruturado.

- Nosso estudo mostra que apesar da terapia convencional o índice de sucesso no controle metabólico do grupo teste foi igual ou superior ao obtido em outros estudos (cf. artigo 1) ressaltando a importância da educação no tratamento do diabetes. Isso fica claro quando analisamos a grande diferença no controle metabólico em relação ao nosso grupo controle. Se levarmos em conta o controle ideal (A1C até 7%), no grupo assistido pelo Centro de Diabetes, 51.4% dos pacientes atingiram tal meta, contra apenas 16.7% no grupo controle. Além disso, ficou mostrado estatisticamente que os pacientes atendidos no Centro de Diabetes apresentaram uma chance 4.38 vezes maior de atingir níveis de A1C até 7%.

4.2 Segundo artigo

- Apesar de mais da metade dos pacientes ter atingido níveis de A1C menores que 8%, apenas 14% conseguiram o controle metabólico ideal (A1C até 7%) e 47% permaneceram com A1C maior que 8%. Talvez se os pacientes tivessem sido submetidos a uma insulinoterapia mais intensiva com utilização de insulinas de ação rápida e automonitorização os resultados pudessem ter sido melhores.

- Uma recente meta-análise que analisou 41 estudos sobre os efeitos da metformina na pressão arterial e perfil lipídico mostrou que apenas a redução dos níveis de colesterol total foi significativa (cf. artigo 2). Nossos resultados corroboram esses

achados e mostram ainda que tal fato não foi dependente da redução do índice de massa corpórea e da circunferência abdominal.

- A não-redução dos níveis de pressão arterial com a metformina em nosso grupo de pacientes está de acordo com vários outros estudos, apesar de existirem relatos de redução da pressão arterial sistólica e diastólica com o uso desta medicação.

- Nossos resultados são concordantes com os da literatura (cf. artigo 2) em relação à ação da metformina na redução do índice de massa corpórea, redução da dose diária de insulina e efeitos adversos relatados com o uso das biguanidas.

5 CONCLUSÕES

- Pacientes portadores de diabetes melito do tipo 1 adultos assistidos por uma equipe multidisciplinar bem estruturada, com ênfase na educação e aderência do paciente e no fornecimento contínuo de insulina, foram capazes de atingir resultados glicêmicos satisfatórios, mesmo sem contar com a automonitorização da glicemia e uso de insulina regular. Os dados deste estudo mostram que é possível obter controle glicêmico satisfatório sem a estrutura complexa utilizada nos tratamentos intensivos com insulina.

- A adição da metformina à insulina possibilitou uma redução significativa de vários fatores de risco da doença cardiovascular mesmo em pacientes portadores de diabetes melito do tipo 2 de longa duração com síndrome metabólica.

6 ANEXO

Nas páginas seguintes serão apresentados em forma de tabelas os dados brutos (*raw data*) coletados durante a pesquisa.

PRIMEIRO ARTIGO - DM Tipo 1: Grupo teste (N = 175)

grupo	idade	genero	dmtempo	imc	medianph	dosesnph	transali	transmed	fpg	A1c	hipoglic	cetoacid
teste	22	m	1	33,8	1,50	2	0	0	122,6	5,4	0	0
teste	52	m	5	24,1	0,36	1	0	0	187,9	7,8	0	0
teste	45	m	15	21,2	1,66	2	0	0	163,4	6,9	0	0
teste	36	m	6	22,0	0,42	1	0	0	117,1	5,2	1	0
teste	38	m	10	23,1	0,68	2	1	1	138,9	6	0	0
teste	30	f	6	19,3	1,23	2	2	0	125,3	5,5	2	0
teste	49	f	22	26,3	1,07	2	1	0	125,3	5,5	0	0
teste	52	m	10	22,7	0,77	2	0	1	168,8	7,1	0	0
teste	49	m	8	22,6	0,86	2	0	0	160,7	6,8	3	0
teste	50	m	10	26,4	0,70	2	2	0	168,8	7,1	0	1
teste	39	f	15	35,3	0,50	2	0	0	149,8	6,4	0	0
teste	21	m	1	25,0	1,38	2	0	0	174,3	7,3	0	0
teste	44	f	8	21,8	0,92	1	0	0	114,4	5,1	0	0
teste	21	m	1	18,1	0,55	1	0	0	133,5	5,8	0	0
teste	55	f	27	25,2	0,89	2	0	0	155,2	6,6	0	0
teste	20	m	0	21,9	2,60	2	0	0	152,5	6,5	1	0
teste	20	f	0	23,2	0,72	2	0	1	168,8	7,1	0	1
teste	62	m	30	20,9	0,30	1	0	0	136,2	5,9	0	0
teste	36	f	8	25,3	1,02	2	0	1	168,8	7,1	0	0
teste	38	f	16	25,3	0,58	1	0	0	217,8	8,9	0	0
teste	63	f	32	30,6	1,62	2	0	0	141,6	6,1	0	0
teste	26	f	4	27,3	0,66	2	0	0	149,8	6,4	2	0
teste	51	f	18	26,2	1,31	2	0	0	155,2	6,6	0	0
teste	64	F	36	37,3	0,32	1	0	0	109	4,9	1	0
teste	40	M	16	28,0	0,37	1	0	0	117,1	5,2	0	0
teste	51	M	7	35,5	0,35	1	1	0	122,6	5,4	0	0
teste	58	M	6	24,4	2,55	2	0	0	198,7	8,2	0	0
teste	64	M	15	32,9	0,58	2	1	0	155,2	6,6	0	0
teste	56	F	24	48,4	0,53	1	0	0	166,1	7	0	0
teste	39	M	14	20,4	1,97	2	0	0	163,4	6,9	0	0
teste	68	f	23	23,4	1,25	2	1	1	152,5	6,5	1	0

teste	28	f	5	20,3	0,85	2	1	0	152,5	6,5	2	0
teste	63	f	14	24,7	0,93	2	0	0	198,7	8,2	0	0
teste	47	f	24	22,6	0,50	1	0	0	261,3	10,5	0	0
teste	29	f	5	15,6	0,80	1	0	0	114,4	5,1	0	0
teste	28	f	7	26,6	0,92	2	0	0	182,4	7,6	0	0
teste	41	f	14	20,8	0,65	1	0	0	114,4	5,1	0	0
teste	25	f	5	20,8	1,30	2	0	0	130,7	5,7	2	0
teste	48	f	14	28,9	1,14	2	0	0	217,8	8,9	0	0
teste	46	f	22	23,4	0,99	2	0	1	106,3	4,8	0	0
teste	66	f	30	20,0	1,27	2	0	0	130,7	5,7	0	0
teste	57	m	24	25,0	0,66	1	0	0	155,2	6,6	1	0
teste	23	m	2	23,0	1,14	2	0	0	163,4	6,9	0	0
teste	32	m	9	28,1	0,76	2	0	0	149,8	6,4	0	0
teste	70	m	26	32,1	0,84	2	1	0	182,4	7,6	1	0
teste	38	m	17	238,0	0,94	2	0	0	111,7	5	0	0
teste	21	m	1	23,7	1,07	2	0	0	155,2	6,6	0	0
teste	35	f	9	21,6	0,93	2	2	0	166,1	7	2	0
teste	53	f	25	29,8	1,42	2	0	0	177	7,4	0	0
teste	24	m	2	24,2	0,69	2	1	0	160,7	6,8	1	0
teste	31	f	3	28,3	0,74	2	0	0	177	7,4	0	0
teste	62	f	29	34,5	0,29	1	0	0	231,4	9,4	0	0
teste	48	f	5	21,5	0,90	2	0	0	130,7	5,7	2	0
teste	75	f	27	30,1	1,67	2	0	0	269,5	10,8	0	0
teste	49	f	27	42,2	1,11	2	0	1	149,8	6,4	0	0
teste	48	m	15	18,6	0,66	2	3	1	136,2	5,9	0	0
teste	46	f	13	32,0	1,00	2	1	1	138,9	6	0	0
teste	64	f	26	50,6	0,68	2	0	0	185,1	7,7	0	0
teste	22	m	1	27,9	1,32	2	0	1	228,7	9,3	0	0
teste	55	f	5	26,7	1,33	2	0	0	157,9	6,7	0	0
teste	67	m	31	25,8	0,91	1	1	0	171,5	7,2	0	0
teste	38	f	13	25,9	0,29	1	0	0	157,9	6,7	0	0
teste	30	m	8	21,9	0,22	1	0	0	136,2	5,9	0	0
teste	52	f	20	24,2	1,29	2	0	0	166,1	7	0	0
teste	56	f	21	41,8	0,68	2	0	0	206,9	8,5	1	0
teste	52	m	19	17,9	0,73	1	0	0	125,3	5,5	0	0

teste	46	f	10	30,8	0,82	1	0	0	147,1	6,3	0	0
teste	55	m	12	37,6	1,27	2	0	0	147,1	6,3	0	0
teste	67	f	23	26,2	1,04	2	0	0	196	8,1	1	0
teste	27	f	6	22,9	1,45	2	2	0	215,1	8,8	0	0
teste	23	f	1	22,7	1,07	2	2	0	111,7	5	0	0
teste	51	f	27	21,9	1,75	2	0	0	190,6	7,9	1	0
teste	68	m	23	22,7	0,69	1	0	0	163,4	6,9	0	0
teste	24	f	3	19,1	1,91	2	1	0	136,2	5,9	0	0
teste	23	m	1	21,5	1,13	2	2	1	168,8	7,1	3	0
teste	27	m	6	22,0	1,03	2	0	0	190,6	7,9	0	0
teste	48	m	13	22,0	0,43	1	0	1	122,6	5,4	0	0
teste	74	m	42	38,1	1,10	2	0	0	269,5	10,8	0	0
teste	23	m	2	24,9	0,90	2	0	1	174,3	7,3	0	0
teste	21	f	1	20,3	1,83	2	1	0	220,5	9	0	0
teste	37	m	15	26,0	1,03	2	1	0	128	5,6	1	0
teste	62	f	21	32,0	0,85	2	0	0	185,1	7,7	0	0
teste	21	m	1	20,2	2,15	2	1	5	128	5,6	0	0
teste	55	f	17	30,8	0,27	1	0	0	163,4	6,9	0	0
teste	28	m	7	28,7	1,10	2	1	0	234,1	9,5	0	0
teste	23	f	3	17,3	1,10	1	0	0	128	5,6	0	0
teste	59	f	13	28,1	1,60	2	0	0	185,1	7,7	2	0
teste	22	m	1	17,3	0,64	1	0	0	198,7	8,2	0	0
teste	43	f	22	23,2	0,76	2	0	0	177	7,4	0	0
teste	56	f	29	28,0	0,33	1	0	0	261,3	10,5	0	0
teste	37	m	15	18,2	0,18	1	1	0	149,8	6,4	0	0
teste	25	m	1	26,3	0,99	2	0	0	185,1	7,7	0	0
teste	39	f	17	21,5	0,47	1	0	0	128	5,6	1	0
teste	24	f	1	19,0	1,46	2	0	0	171,5	7,2	0	1
teste	48	m	16	34,9	1,30	2	0	0	296,7	11,8	0	0
teste	57	m	22	21,5	0,78	2	0	0	163,4	6,9	0	0
teste	56	f	26	25,0	1,56	2	0	0	168,8	7,1	0	0
teste	21	f	1	24,8	1,15	2	1	0	196	8,1	1	0
teste	42	m	22	26,9	1,90	2	0	0	206,9	8,5	0	0
teste	50	m	7	34,0	0,73	1	0	0	128	5,6	0	0
teste	49	m	26	25,4	0,92	2	0	0	190,6	7,9	0	0

teste	25	f	4	20,0	0,45	2	0	1	144,3	6,2	1	0
teste	50	m	10	23,9	0,61	2	1	1	209,6	8,6	3	0
teste	36	f	11	22,8	0,37	1	0	0	274,9	11	0	0
teste	26	f	5	18,7	1,33	2	0	0	185,1	7,7	1	0
teste	50	m	25	23,3	0,94	2	0	0	111,7	5	0	0
teste	46	m	16	22,9	0,78	2	0	0	174,3	7,3	0	0
teste	48	m	7	23,9	0,29	1	0	0	144,3	6,2	0	0
teste	39	m	12	22,4	0,33	1	3	0	258,6	10,4	2	0
teste	29	f	8	29,3	0,67	1	1	2	196	8,1	0	0
teste	32	m	5	30,4	0,89	2	0	0	157,9	6,7	0	0
teste	54	m	25	30,1	1,06	2	5	0	125,3	5,5	4	0
teste	44	f	14	24,6	0,48	1	0	0	160,7	6,8	0	0
teste	66	m	6	21,6	0,38	1	0	0	138,9	6	0	0
teste	22	m	1	30,9	1,58	2	6	0	119,9	5,3	0	0
teste	54	f	17	35,8	0,99	2	0	0	217,8	8,9	0	0
teste	51	f	20	37,1	1,11	2	0	0	130,7	5,7	0	0
teste	46	f	6	28,4	0,14	1	0	0	261,3	10,5	0	0
teste	29	f	8	21,6	0,19	1	0	0	109	4,9	0	0
teste	25	m	2	20,9	1,45	2	0	0	168,8	7,1	3	0
teste	36	f	10	26,9	1,46	2	0	0	190,6	7,9	0	0
teste	26	f	5	26,6	1,48	2	2	0	234,1	9,5	0	0
teste	48	m	16	23,4	1,22	2	0	2	177	7,4	0	0
teste	46	m	10	24,2	1,36	2	0	0	157,9	6,7	1	0
teste	42	m	9	22,1	1,33	2	0	0	193,3	8	0	0
teste	35	m	3	22,7	0,98	1	0	0	114,4	5,1	0	0
teste	41	m	10	28,7	1,32	2	0	0	285,8	11,4	0	0
teste	22	m	1	22,8	1,24	2	3	2	185,1	7,7	0	0
teste	38	m	9	26,1	1,61	2	1	0	201,5	8,3	1	0
teste	57	m	27	37,2	0,82	2	0	0	212,3	8,7	0	0
teste	43	m	21	23,2	0,98	2	0	1	177	7,4	0	0
teste	39	m	11	18,2	1,14	2	0	0	236,8	9,6	0	0
teste	33	f	11	21,9	0,71	2	1	0	190,6	7,9	1	0
teste	23	f	3	22,7	0,62	2	0	1	149,8	6,4	2	0
teste	25	m	4	19,4	0,92	2	2	0	136,2	5,9	1	0
teste	53	m	23	32,0	0,70	2	0	0	283,1	11,3	0	0

teste	56	f	16	35,5	2,47	2	0	0	190,6	7,9	0	0
teste	39	f	13	19,1	0,65	1	0	0	280,3	11,2	1	0
teste	64	f	32	27,6	1,26	2	0	0	283,1	11,3	0	0
teste	23	f	3	10,9	0,95	2	1	0	201,5	8,3	2	0
teste	43	f	17	25,7	0,57	1	0	1	111,7	5	0	0
teste	38	f	7	25,9	1,10	2	0	0	117,1	5,2	0	0
teste	42	m	15	31,6	0,64	1	0	0	114,4	5,1	0	0
teste	49	m	16	27,5	0,82	2	0	0	106,3	4,8	0	0
teste	28	m	7	20,8	1,39	2	0	0	185,1	7,7	0	0
teste	57	m	27	23,5	1,09	2	0	0	114,4	5,1	0	0
teste	49	m	8	28,4	0,50	1	0	0	204,2	8,4	0	0
teste	35	m	13	26,9	1,74	2	0	0	247,7	10	0	0
teste	26	m	2	24,2	0,74	2	0	0	152,5	6,5	0	0
teste	37	f	9	22,4	1,14	2	0	2	122,6	5,4	2	0
teste	43	f	16	24,5	1,45	2	0	0	264	10,6	0	0
teste	58	f	32	38,3	1,94	2	1	0	187,9	7,8	0	0
teste	53	f	13	45,6	1,43	2	0	0	217,8	8,9	0	0
teste	47	f	14	27,5	0,63	1	0	0	149,8	6,4	0	0
teste	52	f	22	32,0	0,89	2	0	0	149,8	6,4	0	0
teste	38	f	10	21,5	1,05	2	0	0	223,2	9,1	0	0
teste	58	f	26	27,4	0,63	2	0	0	111,7	5	0	0
teste	42	f	8	31,3	0,88	2	0	0	174,3	7,3	0	0
teste	21	f	1	22,8	1,20	1	3	0	198,7	8,2	2	0
teste	40	f	16	24,8	1,36	2	0	0	258,6	10,4	0	0
teste	23	f	2	23,8	0,49	1	0	0	149,8	6,4	0	0
teste	49	m	17	24,7	0,83	2	0	0	157,9	6,7	0	0
teste	43	f	17	26,1	0,56	1	0	0	174,3	7,3	0	0
teste	34	f	7	25,7	1,20	2	0	0	160,7	6,8	0	0
teste	29	m	7	20,8	1,43	2	0	0	272,2	10,9	0	0
teste	49	m	9	28,4	0,50	1	0	0	198,7	8,2	0	0
teste	46	m	11	27,4	0,90	2	0	0	234,1	9,5	1	0
teste	34	m	9	23,1	1,06	1	0	0	187,9	7,8	0	0
teste	24	m	2	22,7	0,94	2	0	0	141,6	6,1	1	0
teste	64	f	28	36,3	1,08	2	2	0	264	10,6	0	0
teste	71	m	30	29,4	0,80	1	1	0	122,6	5,4	2	0

teste	34	f	8	35,3	0,79	2	1	0	157,9	6,7	0	0
teste	59	f	17	24,4	1,45	2	1	0	266,7	10,7	0	0
teste	27	f	7	22,5	2,24	2	1	2	160,7	6,8	0	0
teste	62	f	20	30,5	0,29	1	0	0	272,2	10,9	0	0

PRIMEIRO ARTIGO - DM Tipo 1: Grupo controle (N = 30)

grupo	idade	sexo	dmtempo	fpg	A1c	medianph	imc	dosesnph	transali	transmed	hipoglic	cetoacid
controle	45	M	20	222,9	9,1	0,33	26,6	2	1	0	0	0
controle	30	F	6	219,1	8,9	0,72	33,2	2	0	1	0	0
controle	30	F	1	227,5	9,3	0,76	33,2	2	0	0	0	0
controle	46	M	21	233,1	9,5	1,17	32,4	2	1	0	0	0
controle	59	F	16	151,9	6,5	1,87	32,5	1	0	0	1	0
controle	28	M	7	183,7	7,6	1,33	21,5	2	1	1	0	0
controle	32	M	3	180,4	7,5	1,57	33,5	2	1	0	0	0
controle	27	F	6	225,9	9,2	1,81	27,6	2	0	0	0	0
controle	76	F	3	169,1	7,1	0,93	31,7	1	0	0	0	0
controle	32	F	2	246,6	10	1,37	30,3	2	0	0	0	0
controle	33	M	13	176,5	7,4	1,69	33,8	2	1	0	0	0
controle	29	F	8	165,4	7	0,84	33,6	1	0	0	0	0
controle	62	F	23	192,9	8	1,28	32,4	2	0	0	0	0
controle	55	M	20	245,0	9,9	0,99	21,7	2	1	0	1	0
controle	43	F	20	150,8	6,4	1,51	23,8	2	0	1	0	1
controle	21	M	1	180,8	7,5	1,61	24,9	2	1	0	0	0
controle	36	M	16	180,5	7,5	2,08	21,5	2	0	0	0	0
controle	54	F	3	204,8	8,4	0,67	21,5	2	0	0	0	0
controle	43	F	21	227,9	9,3	1,51	27,7	1	0	0	0	0
controle	55	M	10	229,5	9,3	1,61	33,9	2	1	0	1	0
controle	58	F	10	210,5	8,6	2,71	23,3	2	0	0	0	0
controle	32	M	8	185,1	7,7	2,18	29,0	2	1	0	0	0
controle	23	M	2	187,4	7,8	0,82	33,1	2	0	1	0	0

controle	39	F	13	191,4	7,9	2,69	33,6	2	1	0	0	0
controle	49	M	13	233,3	9,5	2,25	28,3	2	0	0	0	0
controle	41	F	15	161,6	6,8	1,84	29,4	1	1	0	0	0
controle	48	F	26	220,6	9	1,25	24,5	2	1	0	0	0
controle	44	F	11	160,7	6,8	0,97	27,8	2	0	0	0	0
controle	55	M	30	233,3	9,5	1,58	24,4	2	0	1	0	0
controle	50	F	26	182,0	7,6	1,18	28,3	1	1	0	0	0

SEGUNDO ARTIGO - DM Tipo 2 (N = 57)

idade	sexo	dmtemp	medmet	imc1	imc2	mednph1	mednph2	fpg1	fpg2	a1c1	a1c2	ct1	ct2	hdl1	hdl2	tg1	tg2	pas1	pas2	pad1	pad2	cint1	cint2
60	M	22	2550	37,7	31,5	1,37	0,7	213,8	194,9	9,6	9,2	211	218	31	45	272	265	140	160	110	110	133	130
61	F	15	1000	31,7	25,1	0,5	0,3	257,3	173,2	11,2	8,4	269	177	28	34	233	173	170	170	80	80	107	107
60	F	18	850	32,8	22,9	0,48	0,6	189,3	132,4	8,7	6,9	234	172	26	48	216	230	160	150	110	80	136	120
44	M	10	1700	30	26,6	1,01	1,1	202,9	175,9	9,2	8,5	184	191	51	43	281	240	120	150	100	80	121	117
71	F	10	850	38,3	31	0,86	0,8	241,0	170,5	10,6	8,3	213	261	49	31	180	197	150	140	90	100	106	127
44	M	18	1700	33,5	26,6	0,53	1	254,6	154,1	11,1	7,7	259	196	47	46	208	284	190	130	90	100	130	107
53	M	11	850	37,8	27,7	0,74	1,1	219,3	192,2	9,8	9,1	244	214	38	41	293	170	170	150	80	70	141	125
62	M	22	2550	37,6	28,3	0,8	1,2	211,1	154,1	9,5	7,7	261	260	34	38	227	181	120	130	80	100	114	113
61	M	18	850	25,9	32,2	0,77	1,1	178,5	197,7	8,3	9,3	265	250	38	46	173	258	130	170	80	70	112	110
66	F	10	850	38,9	35,8	1	0,5	178,5	205,8	8,3	9,6	227	246	29	31	255	264	170	170	80	80	119	106
54	M	9	850	25,6	28,7	0,47	0,5	183,9	205,8	8,5	9,6	220	177	45	48	267	230	120	130	100	80	134	122
57	F	20	1700	32,7	32,2	0,66	0,5	181,2	129,7	8,4	6,8	263	225	43	32	258	225	160	160	110	80	109	106
54	F	10	2550	24,8	32,5	0,48	0,6	232,9	154,1	10,3	7,7	243	223	28	36	259	189	170	150	100	100	116	124
62	M	18	1700	33	21,9	1,43	1,1	202,9	173,2	9,2	8,4	184	173	44	35	225	246	180	150	110	110	123	130
71	F	36	1700	36,5	29,7	0,41	0,8	230,1	137,8	10,2	7,1	224	243	25	38	171	168	150	150	90	110	137	133
51	F	13	850	24	26,4	0,59	0,6	251,9	126,9	11	6,7	178	208	42	29	254	159	120	190	90	90	131	112
67	M	20	850	22,5	24	0,93	0,4	238,3	124,2	10,5	6,6	234	232	49	49	252	253	150	180	100	70	137	112
54	M	17	2550	21,9	32,7	0,61	0,3	241,0	135,1	10,6	7	221	202	37	37	292	269	180	140	80	80	128	126
52	F	10	1700	21,6	30,7	1,24	1	251,9	162,3	11	8	198	229	36	38	210	263	150	130	80	90	116	115
57	F	26	2550	31,3	36,5	0,88	1,1	230,1	146,0	10,2	7,4	190	191	40	30	209	271	180	130	80	70	128	101
45	M	13	850	29,1	26,6	1,11	0,4	230,1	211,3	10,2	9,8	225	188	33	41	187	273	170	160	110	100	140	114
68	M	22	850	35,8	32,9	0,89	0,4	189,3	173,2	8,7	8,4	241	196	33	33	182	198	120	180	80	90	131	99
61	F	12	1700	21,1	22,5	0,55	0,7	194,8	143,3	8,9	7,3	245	172	48	29	299	202	120	190	100	100	124	118
49	F	16	2550	27,8	32,8	0,21	0,2	246,5	124,2	10,8	6,6	182	195	27	47	288	284	170	160	80	70	106	125
59	M	11	1700	35,8	28,6	1,59	0,9	251,9	189,5	11	9	176	200	35	38	267	178	120	160	100	100	131	119
58	F	20	1700	36,1	27,2	1,4	0,9	243,7	178,6	10,7	8,6	245	223	51	32	183	237	140	170	80	100	118	121
59	M	17	850	27,3	32,3	0,66	0,4	227,4	211,3	10,1	9,8	271	235	50	32	211	259	190	190	110	110	120	104
57	F	17	850	33,1	28,1	0,42	0,2	181,2	148,7	8,4	7,5	237	194	47	44	165	181	130	160	90	110	135	104

60	M	27	850	24,8	28,6	0,47	1,1	213,8	154,1	9,6	7,7	230	216	43	46	279	228	190	170	80	90	137	127
54	F	19	1700	24,4	28,3	1,28	1,3	173,0	197,7	8,1	9,3	264	204	31	32	161	194	120	140	80	90	137	128
73	M	21	850	36	28	0,91	1,2	183,9	189,5	8,5	9	237	176	50	30	259	236	190	140	90	100	111	117
61	F	17	850	38,1	35,4	1,33	0,3	246,5	194,9	10,8	9,2	239	184	34	29	250	268	180	150	110	110	121	119
49	M	8	1700	29,9	30,1	0,77	0,7	243,7	200,4	10,7	9,4	213	255	44	35	222	239	190	160	110	110	107	105
56	M	25	1700	30,5	26,6	1,36	1,3	257,3	140,5	11,2	7,2	225	218	35	29	238	278	130	130	100	100	134	106
42	M	7	1700	36,4	26,5	0,34	0,1	194,8	124,2	8,9	6,6	186	226	25	38	258	202	150	170	90	70	105	107
68	F	15	850	25,2	30,9	0,98	0,5	249,2	205,8	10,9	9,6	215	230	37	43	220	188	120	180	80	80	118	121
65	F	20	1700	26,7	24,3	1,11	0,8	175,7	154,1	8,2	7,7	241	222	33	38	297	231	190	130	90	100	106	120
66	M	24	850	32	24,4	1,02	0,6	200,2	140,5	9,1	7,2	199	204	49	37	227	183	140	150	90	110	141	130
62	F	7	850	29,8	33,5	0,81	0,2	200,2	211,3	9,1	9,8	278	240	25	34	295	155	130	190	100	70	118	119
67	M	15	1700	33,9	27,2	0,98	1,3	251,9	151,4	11	7,6	256	203	31	33	259	247	170	160	90	70	119	98
71	F	8	1700	24,2	25,6	1,77	0,8	173,0	126,9	8,1	6,7	225	260	26	42	249	171	190	180	100	80	125	115
61	F	16	1700	34,1	32,1	0,25	0,2	246,5	151,4	10,8	7,6	273	206	33	38	176	226	150	130	90	80	128	115
57	M	12	850	28,3	31,6	0,64	0,7	200,2	159,6	9,1	7,9	237	208	51	48	268	266	170	180	80	110	138	121
61	F	15	1700	34,9	33,6	0,21	1,3	192,1	189,5	8,8	9	211	225	28	49	245	270	180	150	100	80	106	109
60	F	17	850	23,9	23,4	0,63	0,5	224,7	156,9	10	7,8	207	259	30	41	212	207	150	170	80	80	128	123
60	F	15	850	30,6	23,1	0,62	0,7	241,0	181,3	10,6	8,7	202	233	38	33	229	155	170	160	100	90	136	132
39	F	12	1700	34,9	31,1	1,52	0,5	183,9	143,3	8,5	7,3	263	253	37	28	171	267	180	150	80	110	140	120
62	F	10	850	38,6	31,6	0,68	0,1	200,2	194,9	9,1	9,2	239	211	31	49	224	262	150	170	80	100	109	125
74	F	10	1700	25	34,4	0,55	0,7	224,7	181,3	10	8,7	173	219	44	37	198	153	180	190	100	70	121	119
66	F	22	1700	24,2	28,7	0,37	0,5	243,7	151,4	10,7	7,6	240	231	25	36	276	157	190	140	110	90	111	123
66	M	15	850	24	36	0,93	0,1	186,6	159,6	8,6	7,9	251	232	28	34	166	222	140	130	80	100	121	127
46	M	17	1700	37,6	35,5	0,49	0,7	251,9	203,1	11	9,5	279	181	31	33	213	263	190	140	100	100	141	101
53	F	22	1700	22,5	22,2	1,23	1	178,5	156,9	8,3	7,8	245	254	45	41	255	150	190	140	90	110	112	125
58	M	10	1700	33,6	29,7	1,45	0,3	189,3	137,8	8,7	7,1	173	202	43	45	284	189	190	150	110	70	139	127
54	F	15	1700	31,4	24,5	0,53	0,3	189,3	148,7	8,7	7,5	217	192	51	32	266	150	120	140	80	90	140	115
68	F	12	850	32,5	23	0,34	1,3	181,2	208,5	8,4	9,7	218	173	33	45	259	175	180	160	90	70	141	114
63	M	13	850	35,6	26,9	1,43	1	219,3	189,5	9,8	9	275	201	41	41	292	175	170	160	90	100	127	132

7 REFERÊNCIAS BIBLIOGRÁFICAS

1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. 1999.

2. Ministério da Saúde (BR). Secretaria de Assistência à Saúde. Departamento de Assistência e Promoção à Saúde. Coordenação de Doenças Crônico-degenerativas. Manual de diabetes. 2 ed. Brasília: Ministério da Saúde; 1993.

3. Halimi S, Benhamou PY. Diabetes, a worldwide disease. Presse Med 2004;33 Spec No:Sp37-40.

4. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28(2):103-17.

5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977-986.

6. U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837-53.

* * *