UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA

ESTRATÉGIAS PARA MELHORAR O CONTROLE GLICÊMICO ENTRE PACIENTES COM DIABETES MELITO TIPO 2:

UTILIZAÇÃO DE CANETAS PARA APLICAÇÃO DE INSULINA E AUTOMONITORIZAÇÃO DE GLICEMIA CAPILAR

Tese de Doutorado

RAFAEL VAZ MACHRY

Porto Alegre, julho de 2016

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RAFAEL VAZ MACHRY

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito parcial para obtenção do título de Doutor em Endocrinologia.

Porto Alegre, juho de 2016

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ABREVIATURA E SIGLAS

ACCORD	The Action to Control Cardiovascular Risk in Diabetes
ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AMGC	Automonitorização de Glicemia Capilar
BMI	Body Mass Index
BPAID	Problems Areas in Diabetes – Brazil
CG	Control Group
CNPq	Conselho Nacional de Pesquisa e Desenvolvimento
DM2	Diabetes Melito tipo 2
DQOL	Diabetes Quality of Life
DVR	Dimitris Varvaki Rados
FIPE	Fundo de Incentivo à Pesquisa
HbA1c	Hemoglobina Glicada, Glycated Hemoglobin
HCPA	Hospital de Clínicas de Porto Alegre
HPLC	High Performance Liquid Choromatography
IBGE	Instituto Brasileiro de Geografia e Estatística
IDF	International Diabetes Federation
IG	Intervention Group
IMC	Índice de Massa Corporal
Kg/m²	Quilograma por metros quadrados
mg/dl	Miligramas por decilitro
PG	“Pen Group”
PNS	Pesquisa Nacional de Saúde
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCTs	Randomized Clinical Trials
RVM	Rafael Vaz Machry
SD	Standard Deviation
SE	Standard Error
SG	“Syringe Group”
SMBG	Self-Monitoring of Blood Glucose
SUS	Sistema Único de Saúde

T2D	Type 2 Diabetes
TSA	Trial Sequential Analysis
IU	International Units
IU/Kg	Units per kilo
IU/Kg/day	Units per kilo per day
UKPDS	United Kingdon Prospective Diabetes Study
VADT	Veterans Affair Diabetes Trial
WMD	Weighted Mean Difference

RESUMO

A prevalência do Diabetes Melito tipo 2 (DM2) vem aumentando progressivamente e, entre os pacientes acometidos, os idosos compreendem um número significativo. No Brasil, a maior parte da população depende do Sistema Único de Saúde (SUS) para acompanhamento e tratamento do diabetes. O adequado controle glicêmico deve ser alcançado para prevenir ou retardar as complicações crônicas da doença e garantir qualidade de vida. O SUS fornece gratuitamente alguns anti-hiperglicemiantes orais (glibenclamida e metformina) e as insulinas NPH e Regular. Quando em uso de insulinas, a maioria dos pacientes recebe seringas para sua aplicação. As canetas para aplicação de insulina podem ser adquiridas na rede privada de farmácias, e os pacientes receberão gratuitamente os refis de insulina. Apesar de amplamente difundido, este método ainda não é hábito na prescrição da rede pública de saúde, e seu benefício não está bem definido. A realização de aferições frequentes de Glicemia Capilar é muitas vezes solicitada para os pacientes com DM2. Entretanto, o real benefício desta estratégia entre pacientes sem tratamento intensivo com insulina não está bem estabelecido e, por esta razão, o fornecimento de fitas e glicosímetros não é amparado a todos os pacientes no SUS.

Esta Tese de Doutorado tem por propósito avaliar o uso de Canetas para aplicação de insulina entre pacientes idosos com DM2 com controle glicêmico cronicamente inadequado. Incluímos pacientes a partir de 60 anos de idade com Hemoglobina Glicada (HbA1c) superior ou igual a 8,5%. Além disso, avaliamos a realização de Automonitorização de Glicemia Capilar (AMGC) em uma meta-análise de Ensaio Clínicos Randomizados que incluíram pacientes com DM2 em uso apenas de agentes anti-hiperglicemiantes orais, ou em uso de insulina, porém sem tratamento intensivo.

O primeiro estudo refere-se a um cenário frequente para quem trabalha no SUS, que é o paciente já em uso de agentes orais e insulina e que não atinge um bom controle glicêmico e que não tem condições financeiras de adquirir outros medicamentos. Estes pacientes receberam canetas para facilitar a aplicação de insulina. O acompanhamento foi mensal durante 24 semanas, com medidas de glicemia capilar três vezes ao dia. O objetivo inicial foi avaliar pacientes que pareciam não ter solução com acompanhamento em serviço especializado em Diabetes. Foi detectada redução de HbA1c em 2,25% durante o período de estudo. Adicionalmente, ao avaliarmos os valores de HbA1c do final do estudo e compararmos aos valores de seis meses após a conclusão/encerramento do estudo, percebeu-se que houve uma piora glicêmica com retorno aos mesmos níveis elevados de antes da entrada no estudo. A melhora do controle glicêmico obtida durante o estudo permaneceu apenas enquanto o paciente estava em atendimento médico frequente, com medidas multifatoriais, e foi perdida após o encerramento do seguimento, retornando aos antigos valores pré-inclusão.

O segundo estudo se refere a um Ensaio Clínico Randomizado, onde foram incluídos pacientes com características semelhantes ao primeiro estudo, porém estes participantes foram randomizados para permanecer em uso de seringas ou receber canetas para aplicação de insulina. O seguimento foi também por 24 semanas, com consultas mensais e medidas de glicemia capilar realizadas três vezes ao dia. Todos os pacientes receberam os insumos necessários para aplicação de insulina (seringas ou canetas, agulhas, frascos ou refis de insulina). Ao final do seguimento, foi detectada diferença de 0,89% em HbA1c, em favor do grupo que usou canetas. Entretanto, não houve diferença na ocorrência de hipoglicemias ou uso de medicações orais entre os dois grupos. Quanto à qualidade de vida, observou-se deterioração no grupo que usou canetas.

O terceiro estudo refere-se a uma Revisão Sistemática com Meta-Análise de Ensaios Clínicos Randomizados sobre o efeito da realização de AMGC em pacientes com DM2 em uso de agentes orais ou insulina em esquema não intensivo com desfecho de controle glicêmico. Neste estudo, observou que a AMGC pode reduzir os valores de HbA1c temporariamente (redução de 0,34% em 24 semanas, em relação ao controle), principalmente entre os pacientes com valores mais elevados de HbA1c. O método estatístico “Trial Sequential Analysis” (TSA) foi realizado para avaliar os resultados obtidos. Esta análise confirma que os estudos disponíveis na literatura até o presente momento quando em associação podem responder a esta pergunta clínica.

Em conclusão, o uso de medidas multifatoriais (aferição de glicemia capilar, atendimento médico com ajustes frequentes do tratamento e uso de canetas), pode auxiliar no melhor controle glicêmico entre pacientes que pareciam não ter solução no SUS. Isoladamente, o uso de canetas para aplicação de insulina pode ter efeito independente na melhora do controle glicêmico neste grupo de pacientes idosos com DM2. A AMGC pode auxiliar na redução de HbA1c nos primeiros meses de emprego do método, em especial no grupo de pacientes mais descompensados.

APRESENTAÇÃO

Este trabalho consiste na tese de doutorado "Estratégias para melhorar o controle glicêmico entre pacientes com Diabetes Melito tipo 2: utilização de canetas para aplicação de insulina e automonitorização de glicemia capilar", apresentada ao Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul em 20 de julho de 2016. O trabalho será apresentado em 3 partes, descritas a seguir:

1. Introdução / referencial teórico
2. Desenvolvimento

a. Artigo 1: Multifactorial intervention to improve glycemic control among elderly patients with chronically uncontrolled type 2 diabetes users of insulin.

b. Artigo 2: Glycemic control in elderly patients with type 2 diabetes and use of pens for insulin application: A Randomized Controlled Clinical Trial.

c. Artigo 3: Self-Monitoring Blood Glucose improves glycemic control among patients with Type 2 Diabetes without intensive treatment: a systematic review and meta-analysis of Randomized Clinical Trials.

3. Conclusões
4. Perspectivas

INTRODUÇÃO

O Diabetes Melito tipo 2 e senilidade: Atenção à Saúde Pública

O Diabetes Melito tipo 2 (DM2) é uma doença crônica relacionada à deficiência e/ou resistência à ação da insulina nos tecidos periféricos, fazendo com que a glicemia se mantenha elevada. Ao longo da vida, a prevalência dessa doença tende a aumentar (1). Segundo a *International Diabetes Federation (IDF)*, em 2015 havia no Brasil 14,3 milhões de pacientes com Diabetes (entre 20 e 79 anos). Estima-se que, em 2040, esse número irá aumentar para aproximadamente 23,3 milhões de pessoas acometidas em nosso país (2). Conforme a Pesquisa Nacional de Saúde (PNS) de 2013, realizada pelo Instituto Brasileiro de Geografia e Estatística (IBGE) (3), entre pessoas com 60 e 65 anos de idade, 14,5% dessa população tem o diagnóstico de Diabetes. Esse número aumenta para 19,9% quando nos referimos a idade entre 65 e 74 anos. Em comparação aos mais jovem, que tem a prevalência da doença em 5% (menos de 60 anos), estes valores são alarmantes e indicam atenção especial (3).

Em relação ao tratamento, grande parte dos pacientes com Diabetes no Brasil faz seu acompanhamento médico no Sistema Único de Saúde (SUS) – 65,9% declararam que consultam em Unidade Básica de Saúde, Pronto-Atendimentos ou Hospitais Terciários públicos por esta doença (3). Os medicamentos fornecidos gratuitamente para controle do diabetes são Cloridrato de Metformina, Glibenclamida e Insulinas NPH e Insulina Regular em frascos para uso com seringas – retirados diretamente na Unidades Básicas de Saúde. O uso de canetas para aplicação de insulina poderá ser feito caso o paciente adquira a caneta e as agulhas para sua aplicação. Os refis de insulina para uso em canetas são fornecidos no Programa Farmácia Popular do Governo Federal (4).

Controle glicêmico e desenvolvimento de Complicações do Diabetes:

A interferência do controle glicêmico e possíveis alvos para considerá-lo adequado já foram estudados em grandes Ensaios Clínicos. Em 1977, o grupo inglês [UK Prospective Diabetes Study (UKPDS) Group] (5,6) iniciou o desenvolvimento de um estudo multicêntrico recrutando pacientes com diagnóstico recente de DM2. Nos primeiros anos do seguimento, observou-se que pode ocorrer redução do risco de desenvolvimento de complicações microvasculares com tratamento intensivo do Diabetes. Entretanto, este benefício não foi comprovado para complicações macrovasculares entre os pacientes que receberam sulfonilureia ou insulina (5). Mas em um grupo de pacientes obesos que recebeu metformina, observou-se menor risco para infarto agudo do miocárdio e morte por qualquer causa (6). No braço do estudo que avaliou o tratamento com insulina (5), o grupo intensivo chegou a apresentar Hemoglobina Glicada (HbA1c) em média de 7%, já o grupo controle obteve 7,9% nos dez anos de seguimento. Esses valores foram mais baixos nos primeiros cinco anos, com média de 6,6% vs. 7,4%, respectivamente. Apesar dos resultados acima citados, o grupo com tratamento intensivo apresentou maior incidência de hipoglicemias e maior ganho de peso (5). Após a conclusão do estudo primário, os participantes foram seguidos a fim de avaliar desfechos a longo prazo (7). Em 2008, o grupo de pesquisadores divulgou os resultados com mais dez anos de seguimento. Apesar da diferença em HbA1c ter desaparecido já após um ano do encerramento, a redução de risco para complicações microvasculares permaneceu. Além disso, nos grupos que não eram previamente descritos como tendo redução de desfechos (sulfonilureia e insulina), observou-se benefício na redução de risco de infarto agudo do miocárdio, morte por qualquer causa ou morte relacionada ao Diabetes. A redução de risco para esses desfechos no grupo que recebeu metformina permaneceu (7).

Ainda em 2008, outro grupo publicou um Ensaio Clínico na tentativa de esclarecer os desfechos que permaneciam duvidosos nas primeiras publicações do

UKPDS. O estudo “The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation – ADVANCE” (8) avaliou pacientes já com complicações crônicas ou com fatores de risco para doença vascular. Os pacientes possuíam o diagnóstico de Diabetes com duração média de aproximadamente oito anos, e idade média de 66 anos. Os participantes foram randomizados para tratamento intensivo com Gliclazida e outras medicações necessárias, ou tratamento convencional. O alvo do tratamento intensivo era alcançar HbA1c menor ou igual a 6,5%. O seguimento médio durou cinco anos, com média de HbA1c final próxima a 6,5% e 7,3% nos grupos intensivo e convencional, respectivamente. Apesar da redução do desfecho combinado (complicações macrovasculares e microvasculares), isoladamente não houve diferença em relação a complicações macrovasculares entre os grupos. Entretanto, ocorreu maior número de hipoglicemias não graves e graves no grupo de tratamento intensivo (8).

Outro grupo publicou, em 2009, o “Veterans Affairs Diabetes Trial – VADT” (9). Este estudo também comparou o tratamento intensivo com tratamento convencional para avaliar risco de complicações do diabetes e mortalidade. Foram incluídos pacientes com HbA1c maior que 7,5%, independente da presença de complicações crônicas do diabetes. Para o grupo intensivo, foram iniciadas metformina e rosiglitazona para os casos de Índice de Massa Corporal (IMC) superior a 27 kg/m², ou glimepirida e rosiglitazona para os pacientes com menos peso. Ambas as drogas em doses máximas. Se o paciente não alcançasse HbA1c menor que 6%, era iniciada insulina. Já no grupo convencional, as mesmas drogas eram iniciadas com metade da dose, e a insulina era iniciada se HbA1c estivesse maior que 9% no seguimento. Porém, 52% dos pacientes já usavam insulina na inclusão do estudo. Quarenta por cento deles já tinha história de eventos cardiovasculares e 62% de complicações microvasculares. A mediana de seguimento foi de 5,6 anos. Este estudo não apresentou diferenças em relação ao desenvolvimento de complicações

microvasculares, macrovasculares ou mortalidade (9). Em 2015, o mesmo grupo de pesquisadores publicou o seguimento de 92,4% dos pacientes incluídos no estudo original. Com mais 9,8 anos de acompanhamento sem intervenção, o grupo inicialmente intensivo apresentou menor risco de eventos cardiovasculares maiores, porém sem redução de mortalidade (10).

O estudo “The Action to Control Cardiovascular Risk in Diabetes – ACCORD” (11), publicado em 2008, também tinha por objetivo avaliar o desenvolvimento de complicações em relação ao tratamento. Pacientes com idade média de 62,2 anos, e duração de diabetes com mediana de 10 anos, foram randomizados para tratamento intensivo e eram avaliados com maior frequência, com o objetivo de reduzir a HbA1c para menos que 6%, ou acompanhamento convencional. Entre todos os pacientes, 35% já haviam relatado algum evento cardiovascular prévio. O estudo foi descontinuado com 3,5 anos de duração, com o grupo intensivo alcançando HbA1c em torno 6,4% em média e grupo convencional, 7,5%. O grupo intensivo apresentou maior mortalidade para qualquer causa, com taxas menores de infarto não fatal, porém mais altas para mortalidade de causa cardiovascular. Este grupo também apresentou maiores taxas de hipoglicemias, aumento de peso e retenção de fluidos (11). O seguimento de cinco anos após suspensão do estudo confirmou os resultados anteriores, mesmo não mantendo níveis tão estritos de HbA1c (12).

Em resumo, há grandes Ensaio Clínicos para avaliar risco de complicações do DM2, tendo como intervenção o grau de intensidade do tratamento e alvo glicêmico. Entretanto, em análise conjunta destes estudos, há variedade de metodologias e estratégias empregadas. Desde o UKPDS (5-7), que incluiu apenas pacientes com diabetes recém diagnosticado, até os demais com pacientes já com complicações crônicas. Podemos concluir que, apesar de efeitos adversos como hipoglicemia, o controle glicêmico adequado muda desfechos no futuro, dependendo da intensidade e tempo de acompanhamento. Alguns pacientes, como aqueles de alto risco

cardiovascular, deverão ter seu alvo glicêmico personalizado a fim de evitar deterioração clínica.

Quanto ao tratamento proposto, os estudos também variam. Usuários de insulina foram incluídos nas análises, porém com grande heterogeneidade na proporção desses pacientes. No ADVANCE (8), apenas 1,5% dos pacientes avaliados usavam insulina, já nos estudos ACCORD (11) e VADT (9), 35% e 52%, respectivamente utilizavam insulina. Apenas o estudo ACCORD (11) fez menção a medidas não farmacológicas para o grupo intensivo, como consultas mais frequentes e atendimento individualizado. Em relação ao tipo de medicamento para alcançar o controle glicêmico, um estudo de meta-análise *network* avaliou a introdução de drogas para o tratamento do diabetes. Não houve diferença entre as classes, nem mesmo quando se usa insulina, para alcançar o controle glicêmico satisfatório (13).

Uso de Canetas para facilitar a aplicação de insulina:

O uso de canetas para aplicação de insulina significou evolução no manejo do Diabetes. A facilitação para aplicar insulina poderá auxiliar na acurácia da dose prescrita e aderência ao tratamento, além de facilitar no transporte e rotina diária, melhorando a qualidade de vida, principalmente entre pacientes idosos (14-18). Apesar disso, esses dados são oriundos de estudos observacionais. Até então, não identificamos estudos de intervenção com avaliação de qualidade de vida ou aderência para o uso de insulinas NPH e Regular (fornecidas pelo SUS). Além disso, a maioria dos estudos usou dispensação farmacêutica como medida de uso de insulina, o que pode não fornecer um dado preciso para análise de adesão ao tratamento (16-18). Nestes estudos, os dados utilizados para avaliação de aderência foram pelo número de refis ou frascos retirados nas farmácias, não necessariamente utilizados na prática.

As canetas estão disponíveis para uso tanto com insulina NPH, Regular, quanto com análogos de insulina isoladamente ou em pré-misturas. A insulina é comercializada em pequenos refis de 3 ml (100 UI/ml). Estes são colocados dentro do dispositivo e deverão ser trocados a cada trinta dias caso não sejam utilizados completamente. Não há necessidade de refrigeração nesse período. Algumas canetas são descartáveis e são comercializadas carregadas (para análogos de insulina). As agulhas para aplicação são adquiridas independentemente com o mesmo calibre das disponíveis para seringas (4 a 8 mm). O paciente, a cada aplicação, deverá ajustar a dose prescrita no êmbolo da caneta, podendo auxiliar-se do dispositivo visual ou auditivo (cliques) a cada unidade. Os cuidados de higiene e aplicação são os mesmos que para os usuários de insulina. Caso o paciente não utilize pré-misturas de insulinas já prontas, não poderá misturar insulinas em uma mesma aplicação da caneta, diferente dos usuários de seringas.

Os resultados quanto ao controle glicêmico, aderência e qualidade de vida entre os usuários de canetas necessitam ser avaliados, a fim de reconhecer o real benefício da troca de seringas por canetas entre os usuários de insulina. O uso destes dispositivos entre idosos poderá auxiliar no manejo daqueles com dificuldades para alcançar o controle glicêmico satisfatório. A avaliação deste desfecho é um dos objetivos desta Tese de Doutorado.

Automonitorização de Glicemia Capilar e controle glicêmico:

A realização de Automonitorização de Glicemia Capilar (AMGC) entre pacientes com DM2 muitas vezes é indicada na prática clínica. Entretanto, o real benefício desta estratégia ainda não é bem compreendido para este grupo de pacientes. Algumas meta-análises já tentaram agrupar os estudos realizados para este fim, apenas com pacientes sem usar insulina (19-24). A última disponível, publicada

em 2012 (24), agrupou dados individuais de 2552 pacientes, incluídos em seis Ensaios Clínicos. Neste estudo, houve redução de HbA1c em 0,18% aos três meses e 0,23% aos 12 meses de seguimento, em favor da realização de testes de glicemia capilar. Após esta publicação, vários outros estudos menores já foram publicados (25-31).

No SUS, o fornecimento de fitas reagentes não é feito a todos os pacientes. Classicamente, esta dispensação é feita para pacientes com Diabetes Melito tipo 1 (DM1) (4). Cada município poderá incluir outros critérios para este fornecimento. Em Porto Alegre, por exemplo, os critérios estabelecidos pela Secretaria Municipal de Saúde são: pacientes com DM1, gestantes com Diabetes, DM2 em uso de dois tipos de insulina (basal-bolus), DM2 em uso de pelo menos um tipo de insulina se em caso de transplantados ou indivíduos com mais de 65 anos (32).

A AMGC poderá exigir do paciente mais atenção à sua doença, e facilitar a percepção de hipoglicemias em virtude do tratamento ou hiperglicemias após omissão de cuidados ou hábitos não considerados saudáveis. Por outro lado, também poderá causar mais estresse em relação à doença, pelo compromisso restritivo de fazer as aferições solicitadas pelo médico (19). Em virtude destes pontos, o real benefício desta estratégia, principalmente entre pacientes que não fazem tratamento intensivo para o Diabetes, precisa ser mais bem definido.

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ARTIGO 1

Multifactorial intervention to improve glycemic control among elderly patients with chronically uncontrolled type 2 diabetes users of insulin.

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Abstract:

Background / Objectives: The prevalence of diabetes among older adults is increasing. Many of them do not have adequate glycemic control despite extensive already established therapy. The objective is to find strategies to management of older patients with type 2 diabetes without adequate glycemic control despite extensive therapy, especially in public health systems.

Design: prospective, non-randomized, quasi-experimental study

Setting: a Brazilian tertiary hospital

Participants: We included 45 patients over 60 years old, both sexes, with Glycated Hemoglobin (HbA1c) >8.5% using oral hypoglycemic agents and insulin.

Intervention: Syringes were replaced by pen devices. All patients received blood glucose monitor and capillary blood glucose tests.

Measurements: HbA1c was measured at baseline, 12 and 24 weeks. Blood pressure levels, number of medicines used, incidence of hypoglycemia and adherence were evaluated monthly. All patients underwent questionnaires to assess quality of life and impact of this measure.

Results: HbA1c, at baseline was 10.34 ± 0.22%, similar to the values one year and 24 weeks prior to inclusion, and it was 8.54 ± 0.24% and 8.09 ± 0.21%, after 12 and 24 weeks after intervention, respectively, with significant reduction from baseline. Moreover, we found no difference in the occurrence of hypoglycemia from baseline to the end of the study. Quality of life and psychological stress did not change during this study.

Conclusion: More frequent medical visits, with treatment inputs including the use of pen devices and self-monitoring improved glycemic control (reduction of 2.25% in average HbA1C at 24 weeks) with no significant increase in hypoglycemia. Our data support a

change in the management and medical attitude of elderly patients with chronically decompensated diabetes.

Key Words:

Elderly, Diabetes, Pen Device, Self-Monitoring Blood Glucose, Glycemic Control.

Introduction:

Elderly patients may need multiple medications for treatment of comorbidities. Patients with type 2 diabetes (T2D) can need to use insulin as part of intensive treatment to achieve adequate glycemic control. In Brazil, according to Vigitel 2015 – a population based study, the number of patients with diabetes is increasing, and at 65 years of age, approximately 24.4% of people reported having diabetes in 2014 (1). Nevertheless, the care of these patients is hampered by access to ongoing medical monitoring and new therapeutic technologies. A large study with T2D patients showed that only 26% of them had good glycemic control in the public healthcare system (2).

It is essential to ensure adherence to treatment in order to achieve satisfactory glycemic control. The association of different classes of drugs (e.g., antihypertensive, antidiabetic agents and statins) may influence adherence (3). Older patients tend to have higher compliance rates than younger ones (3). However, older patients may have difficulty in using devices to administer insulin, which may prove an obstacle for adequate adherence to injection therapy (4). Approximately 35% of patients with diabetes do not report insulin application rates, and the main causes are fear of frequent hypoglycemia and difficulty in applying the injections (4).

According to some studies, patients using pen device have better rates of treatment adherence. Furthermore, there is greater satisfaction when this method is used instead of the syringes (5). Patients using pens relate more easily to insulin delivery and fewer report pain on application (6).

Pawaskar *et al* (7) studied patients using a syringe compared to pen users and observed that syringe users had higher health care costs, although expenditures directly on the insulin delivery method are higher for pen users. However, the answer to replacement of syringes by pens in elderly patients with chronic decompensated diabetes in Clinical Trials is not known.

To evaluate elderly with diabetes patients treated in the public healthcare system who are already using high doses of insulin and remain without adequate glycemic control for long time, we developed this study including patients from 60 years or older with chronically uncontrolled diabetes already being monitored at a tertiary hospital. Conventional medical care of all patients was replaced by monthly medical follow up with frequent adjustments of treatment, use of pens for insulin delivery and Self-Monitoring Blood Glucose (SMBG) daily.

Methods:

Study Oversight:

This is a quasi-experimental study to examine a multiple intervention to improve the glycemic control, including the replacement of syringes by pen devices for insulin use in elderly patients with T2D without adequate glycemic control in a Brazilian tertiary hospital. The Research Ethics Committee of the Hospital de Clínicas de Porto Alegre approved the study protocol. All participating patients provided written informed consent. Funding was provided by Conselho Nacional de Pesquisa (CNPq) – Brazil and Fundo de Incentivo à Pesquisa (FIPE) at Hospital de Clínicas de Porto Alegre.

Study Population:

We selected patients consecutively from the Diabetes Section – Endocrinology Division of Hospital de Clínicas de Porto Alegre or who were named by medical assistants from other clinical specialties. Patients were included between June and December 2014.

Inclusion criteria: patients with T2D and sixty years or older, already using insulin (NPH ± Regular) with syringes in addition to at least one oral antihyperglycemic agent. HbA1c should be equal or greater than 8.5%, collected less than three months

before. Exclusion criteria: declaring themselves unable to self-administer insulin or having a lower glomerular filtration rate than 30 ml/min/1.73m^2 by MDRD equation.

Intervention:

All participants received pen devices for insulin delivery, blood glucose monitor and lancets. Patients were instructed on the use of insulin, self-application and storage of insulin. Follow-up lasted six months, with monthly visits. At each visit, all received insulin refills and capillary blood glucose tapes (3 tests/day), and returned the used refills in the subsequent visit to control non-used units. We removed the remaining amount of refills to calculate the number of units of insulin used in the last month.

In the first month, patients continued to use the same prescribed insulin dose as prior to enrollment. After this, adjustments began to be made based on capillary blood glucose notes according to the protocol or evaluators judgment.

We considered appropriate fasting capillary glucose between 70-130 mg/dl. To improve the morning control, the evening dose of insulin NPH was adjusted by increasing or decreasing the previously prescribed dose by 4 IU. To adjust the glycemic control before lunch and dinner, the same change was made in the morning dose of insulin NPH. In case of use of high-dose insulin NPH (greater than 40 IU in each application), the insulin Regular was adjusted, as adjustment of insulin NPH or insulin Regular was initiated (initial dose of 4 IU) before breakfast, lunch or dinner (depending on periods without adequate glycemic control). For patients who were only on bedtime insulin NPH and needed to receive another injection in the morning, NPH was begun with 12 IU before breakfast.

We asked questions about weekly hypoglycemias and other adverse effects. We have reviewed number of medications, antihypertensive drugs, oral antihyperglycemic agents and number of pills taken daily. Blood pressure was measured twice on each arm, calculating the average value, after relaxing in a sitting

position for ten minutes. Anthropometric measures of weight, height and body mass index (BMI) were calculated (kg/m^2).

BPAID (Problems Areas in Diabetes – Brazil) and DQOL (Diabetes Quality of Life) questionnaires were performed, both validated versions in Portuguese. The questionnaires used do not have a standardized cut-off point (8,9). The first evaluates emotional stress related to Diabetes in 20 questions. In the second, we used the variables "impact" and "satisfaction" to evaluate quality of life. Other standard variables in this questionnaire are not applicable to the population studied. There were 33 questions. These Questionnaires were applied in the first and last visit.

Laboratory Evaluation:

HbA1c (HPLC ion exchange) was measured at baseline, 12 and 24 weeks after inclusion. We also looked at the medical records to evaluate the measures of HbA1c (same method) at least one year before and six months after the intervention.

Study Endpoints:

The primary endpoint was the reduction of HbA1c in 12 and 24 weeks. Secondary endpoints were the reduction of the number of hypoglycemia or the presence of nocturnal, asymptomatic or severe hypoglycemia, reduction of blood pressure levels and improving quality of life. We also evaluated the degree of compliance. Adherent patients were those who used at least eighty percent of the prescribed daily dose in most months, as usually done in clinical studies (5,10,11).

Statistical analysis:

To calculate the sample size of 42 patients, we expect improvement of at least one percent after the use of insulin in the pen device from baseline. We use a power of 90% and alpha error of 5%. All analyses were performed on an intention-to-treat basis.

Normality test was conducted for Shapiro-Wilk test to evaluate the distribution of the sample.

Continuous variables with normal distribution were described as mean and standard error (SE) and categorical variables as number of cases (percentage). To compare groups with continuous variables, we used the t-Student test. To compare all variables using the same sample, modified in time, categorical variables were analyzed by chi-square test and analysis of continuous variables for repeated measurements was performed by Generalized Estimated Equation with Bonferroni correction. Analyses were done using SPSS 18.0 software (Chicago, IL).

Results:

Study population and treatment:

Forty-five patients were included, 35 of whom completed the follow-up. Six patients dropped out because they did not like the study protocol. One patient had acute myocardial infarction requiring myocardial revascularization surgery and subsequent prolonged hospitalization for surgical site infection. One patient required hospitalization for hip prosthesis infection. One patient suffered lower limb amputation for diabetic foot and another died without a definite cause during psychiatric hospitalization for alcoholism.

The patients' medical records or the questions asked on the first visit evaluated social and demographic characteristics and medical conditions at baseline and were described in Table 1.

Diabetes control:

The average HbA1c was 10.34 ± 0.22% at baseline. At 12 weeks follow-up, HbA1c was 8.54 ± 0.24% ($p < 0.001$). In 24 weeks, HbA1c was 8.09 ± 0.21%

(difference from baseline $p < 0.001$). There was no difference between the 12 and 24 weeks ($p = 0.402$) (Figure 1). There was HbA1c reduction of 2.25% during the intervention period. And 1 year before inclusion, HbA1c was 10.08 ± 0.32% and 24 weeks before it was 10.46 ± 0.32%. We monitored the medical care of patients after the conclusion of study, and the average HbA1c was 9.77 ± 0.34% and 9.46 ± 0.46% at 12 and 24 weeks after conclusion, respectively, with no difference when compared to baseline values (Figure 1).

Additionally, we compared patients who used sulfonylurea (14 patients) to those who did not use it (31 patients): The HbA1c values at baseline were similar to each other (10.3 ± 1.38% vs. 10.4 ± 1.59%, $p = 0.83$). However, after 24 weeks of follow-up, patients using sulfonylureas showed a tendency of greater reduction (-2.42 ± 1.49% vs. -1.54 ± 1.86%, $p = 0.43$), although that was not significant. There was no increased incidence of hypoglycemia between the groups. We found no difference among the prescribed dose of NPH, Regular or Regular/NPH insulin ratio between between users and no users of sufonylyrea.

Clinical Outcomes:

Considering the incidence of hypoglycemia per week, we found a frequency lower than 1 time/week [mean 0.8 per week (hypoglycemia reported one month before the inclusion)]. These values did not change during the study, ($p = 1.00$). We detected a reduction in the number of patients with asymptomatic hypoglycemia ($p = 0.024$), but no difference was found among the number of patients with nocturnal ($p = 0.07$) or severe hypoglycemia ($p = 0.25$) during follow-up (Figure 2).

During follow-up, there was an increase in the average number of medicines used from the fourth month onwards, but not due to the number of antihypertensives or antyhyperglycemic agents, which remained similar during the study. Maybe other classes of drugs can explain this fact (antidepressants, analgesics or especific

treatment to other comorbidities). Systolic and diastolic blood pressure levels did not change during the study.

In the entire group of patients, there was an increasing of prescribed dose of insulin (IU/kg) from third month and Regular/NPH insulin ratio, but the patients' BMI remained similar to the initial one throughout the study (Figure 3).

We analyzed adherence to prescribed insulin dose: Patients used 70.07 ± 3.74% in mean of the prescribed insulin dose during the first month of study. At subsequent visits, all means were greater than 80% (Figure 4).

Additionaly, we evaluated the response to early intervention considering "responders" patients who reduced HbA1c at least 0.5% in the first trimester of follow-up. Compared to "non-responders", those patients used more sulfonylureas associated with metformin and insulin ($p = 0.001$) and had higher rates of hypoglycemia until the sixth visit ($p = 0.009$), with no differences in severity and presence of nocturnal or asymptomatic hypoglycemia.

Quality of life:

We compared pre and post intervention. Scores presented for BPAID were 39.44 ± 3.66 and 34.62 ± 4.24 (at baseline and in the end of study, respectively, $p = 0.107$). When we stratified by domains, related to "emotions", "food", "treatment" and "social", there also were no differences. In DQOL we used the variables "impact" and "satisfaction". For variable "impact" the score were 2.27 ± 0.11 and 2.43 ± 0.12 ($p = 0.109$). For variable "satisfaction", scores were 2.45 ± 0.12 and 2.57 ± 0.13 ($p = 0.109$).

Discussion:

In this study lasting 24 weeks, the multifactotial intervention including replacement syringes for pens for insulin application and implementation of frequent

SMBG, with monthly adjustment of the treatment were effective to improve glycemic control among elderly patients with uncontroled T2D.

In our study, all patients were treated in a public Hospital and they were already using high doses of insulin and all were chronically uncontrolled despite of the efforts of the health care team, therefore another measure to improve glycemic control was needed. We developed a protocol to change the benefit system without necessarily adding another oral medication. Compared to large clinical trials with T2D, we found higher levels of HbA1c in the beginning of the study (VADT trial with approximately 9.4%, ACCORD trial with 8.1% and ADVANCE trial with 7.2% at baseline). In general, these studies also had the possibility of introducing other oral medication or starting insulin (12, 13, 14).

A study performed in basic health care (15), with adjustments in the treatment of diabetes monthly including SMBG did not find any improvement in glycemic control in the entire group of patients. When these authors considered only patients with HbA1c greater than 7% at baseline (mean 8.6 ± 1.5%), even in this group, no improvement in glycemic control was observed. The initial HbA1c average was lower in this group of patients than in our study and only 21.19% of patients were using insulin. However, many other clinical characteristics were similar, and unlike this study, in our follow-up, we provided insulin, pen devices, and ask to conduct more frequent blood glucose tests. Thus, possibly the use of pens may have positively influenced the better results we found.

Previous studies described users of insulin as having lower rates of adherence compared to users of oral medications for diabetes treatment (7,16). Adherence to treatment with insulin is usually lower than 75 percent in patients starting insulin (11,16). However, observational studies including patients who have used insulin for a longer time, showed similar rates of adherence among patients using syringes or pens,

both greater than 80 percent. The long-term use of insulin delivery methods, regardless of pen or syringe, appears to be related to improved adhesion (7,10). Moreover, older patients seem to exhibit better adhesion rates than younger subjects (5). However, most of these studies are observational, counting refills dispensed at the pharmacy, according to medical prescription, to measure adherence (10,16). In the present study, the method for adherence appears be more precise, the amount of units of insulin in each refill was counted in our study. Regardless, we found higher rates of adherence to treatment as described in the literature from the second month of follow-up.

Another factor that may have justified a significant improvement in glucose control was the possibility of frequent adjustments of insulin. In general, prior to inclusion, patients were seen every 4-6 months, too long a time between assessments. During follow-up, we can adjust the prescribed dose of insulin every month based on the capillary blood glucose. When this intervention was suspended, even keeping patients on the pen device, the level of HbA1c returned to similar values at the baseline.

SMBG may also have contributed to the improvement in glycemic control, but not all results can be justified by this management alone. Results presented in previous studies are inconsistent due to the variety of methodologies and different frequencies of measurements of capillary glucose. Our patients underwent three measurements daily. As to patients who were not using insulin, a systematic review with meta-analysis showed a slight reduction in favor of SMBG, however, with multiples protocols of capillary glucose (17). In users of insulin, Nauck *et al* (18) evaluated the performance of SMBG in four measurements weekly, in patients who underwent conventional insulin treatment (basal or pre-mixtures), and found no difference in HbA1c. In contrast, Murata GH *et al* (19) conducted a non-controlled study similar to ours regarding the frequency of performing blood glucose tests. Patients underwent four daily measurements, the follow-up with intervention was short (only eight weeks), but with a

decrease of approximately 0.3% in HbA1c in this period. This result was sustained up to 52 weeks of follow-up post-intervention. Chen *et al* (20), found a 1.85% reduction of HbA1c at 28 weeks; on the contrary of other studies, the initial average HbA1c was higher, around 9.54%. The magnitude of HbA1c reduction found in our follow-up was not reported in any other previous study. Possibly patients with higher HbA1c levels can have greater benefits from more frequent SMBG. I-Chin Huang *et al* (21), showed a negative correlation between the number of daily blood glucose tests and the presence of chronic complications of diabetes, as well as with the level of HbA1c.

Usually, insulin is the third drug included in T2D treatment in the Public Health System in Brazil, with free distribution, after attempting treatment with metformin and sulfonylurea. A systematic review and network meta-analysis assessed the potential reduction of HbA1c with various classes of drugs such as a third drug. Although the results were similar between oral drugs and insulin, original studies used much lower doses of insulin than are usually necessary for patients with very poor glycemic control, as in our study. Perhaps the effect of insulin has been underestimated (22). Current evidence reinforces the conduct to maintain sulfonylurea treatment of patients with T2D when there is secondary failure with these drugs, making it necessary to associate insulin (23-25). However, we received some patients who were not yet using this drug, and in use of high doses of insulin. In this situation, we did not add sulfonylurea in order not to alter the study protocol. Additionally, there was no suspension of sulfonylurea, only adjusting the insulin dose. Although the results did not show a difference in HbA1c between patients who used sulfonylurea or not, there is a visible tendency to greater reduction during follow-up among patients using this drug. We believe that, regardless of the prescribed dose of insulin, the maintenance of sulfonylurea may help control glycemia.

A possible limitation was the absence of a control group to evaluate the effect of using pens for insulin delivery. On the other hand, our objective was to evaluate a

multifactorial strategy to improve glycemic control in chronically decompensated patients treated in the Brazilian Public Health System. One year prior to enrollment, with conventional medical care, patients did not have satisfactory glycemic control. We also realized that patients found it extremely difficult to understand the questionnaires; even with poor glycemic control at baseline, they said that were very satisfied with the result of their treatments, clearly showing scant understanding of their glycemic control and disease. Although several of them said that they preferred to use pens, we can not measure this information with validated instruments.

We found no difference regarding hypoglycemia events. However, the average of HbA1c levels was higher in the beginning of the study and, even lower than baseline; the final values were well above the target. Therefore, if more patients had reached the HbA1c levels near 7%, possibly we would have more hypoglycemic events per patient. During the ACCORD trial (13), the group achieved HbA1c on average 6.4%, compared with the group who achieved HbA1c on average 7.5%; therefore, they had higher rates of hypoglycemia and for that reason needed medical care. In addition, achieving very low levels of HbA1c among high-risk patients has increased mortality, but the rationale for this remains unexplained (26).

In conclusion, intensive follow-up with strategies to increase accessibility to treatment improves glycemic control in elderly subjects with T2D, and strategies to ensure adherence to treatment can help in this goal among patients who appeared to have no solution. The individual effect of each strategy still needs to be better clarified.

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Disclosure:

All authors have no conflict of interest to declare.

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TABLE 1:

Table1. Baseline Characteristics of the Study Population. *mean ± SD or (%)*

Variables	Measurements
Age in years *(mean ± SD)*	66.71 ± 4.11
Male sex (%)	28.9
Race (%)	
White	62.2
Black	24.4
Other	13.3
Religion (%)	
Catolics	73.3
Evangelics	13.3
Spiritualists	4.4
Others	8.8
Family Income (%)*	
up to 1 minimum wage	17.8
1-2 minimum wages	48.9
over 2 minimum wages	33.3
Years of education in years (%)	
uneducated or less than 1 year	8.9
1 to 3 years	15.6
4 to 8 years	40.0
9 years or more	35.6
History of smoking (%)	
Never smoking	60.0
current smoking	-
Former	40.0
Alcohol consumption (%)	
Never drinking	60.0
Social Considers	28.9
Alcohol abusers	02.0
Former	09.1
Diabetic Retinopathy† (%)	
Absent	11/37 (29.7)
Mild or moderative Non proliferative	11/37 (29.7)
Severe Non proliferative	04/37 (10.8)
Proliferative	11/37 (29.7)
Diabetic Nefropathy‡ (%)	
Absent	17/40 (42.5)
Albuminuria increased	15/40 (37.5)
Albuminuria greatly increased	07/40 (17.5)
Nefrotic Albuminuria	01/40 (02.5)
Diabetic Neuropathy‡ (%)	
Absent	20/39 (51.3)
Present	19/39 (48.7)
Presence of cerebrovascular disease§ n and (%)	02/40 (05.0)
Presence of ischemic cardiopathy‖ n and (%)	13/43 (31.0)
Time of Diabetes in years (*mean ±SD)*	15.93 ± 7.8
Time using insulin in years (*mean ±SD)*	9.53 ± 6.03
Glycated hemoglobin (*mean ±SD)*	10.34% ± 1.53
Positive familiar history for Diabetes (%)	64.4
Presence of Hypertension (%)	93.3
Sulfonylurea use (%)	31.1
Time of Hypertension in years (*mean ±SD)*	16.02 ± 11.09
Number of use medicins (*mean ±SD)*	8.42 ± 2.32
Number of antihypertensive (*mean ±SD)*	3.52 ± 1.08
Number of use tablet (*mean ±SD)*	14.46 ± 6.42
Insulin dose per kg / day (*mean ±SD)*	0.85 ± 0.48
Regular insulin use (%)	31.1
Body mass index (weight / height 2) (*mean ±SD)*	31.70 ± 4.88
Systolic blood pressure in mmHg (*mean ±SD)*	138.77 ± 19.15
Diastolic blood pressure in mmHg (*mean ±SD)*	70.09 ± 11.00

*minimun wage iqual to $ 220,70 (reference year = august/2015)

†chart review

‡chart review; we consider albuminuria >14mg/g of Creatinine (albuminuria increased) and >140 mg/g of Creatinine (albuminuria greatly increased), and neuropathy to patients with description of positive monofilament test, sensorial changes or suggestive lesions.

§history of Transient ischemic attack or stroke.

||history of unstable angina, acute myocardial infarction or diagnosis of ischemic heart disease

FIGURES:

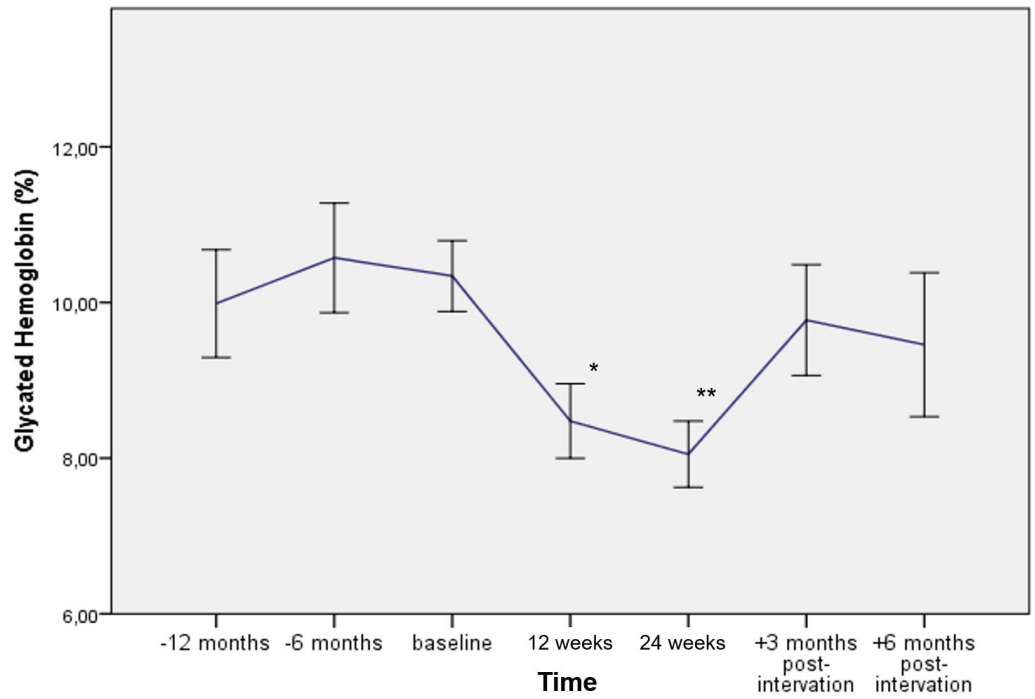

Figure 1. Glycated Hemoglobin before, during and after de follow-up. Mean ± SE.
* Compare with baseline p < 0.001 ** Compare with baseline p < 0.001, compare with 3 months p = 0.402

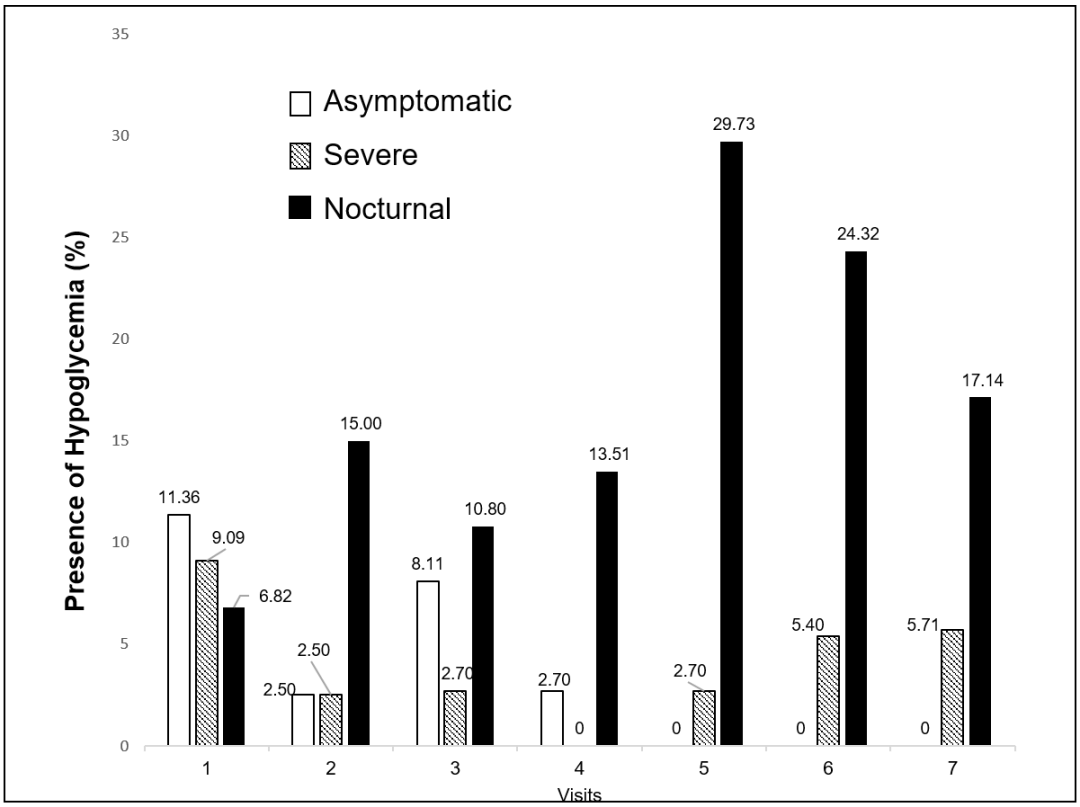

Figure 2. Presence of assyntomatics, severes and nocturnals hypoglycemias (%). In the first visit, the patient reported about a month prior to enrollment. Other visits, dates based on glycemic daily notes and reported by patients.

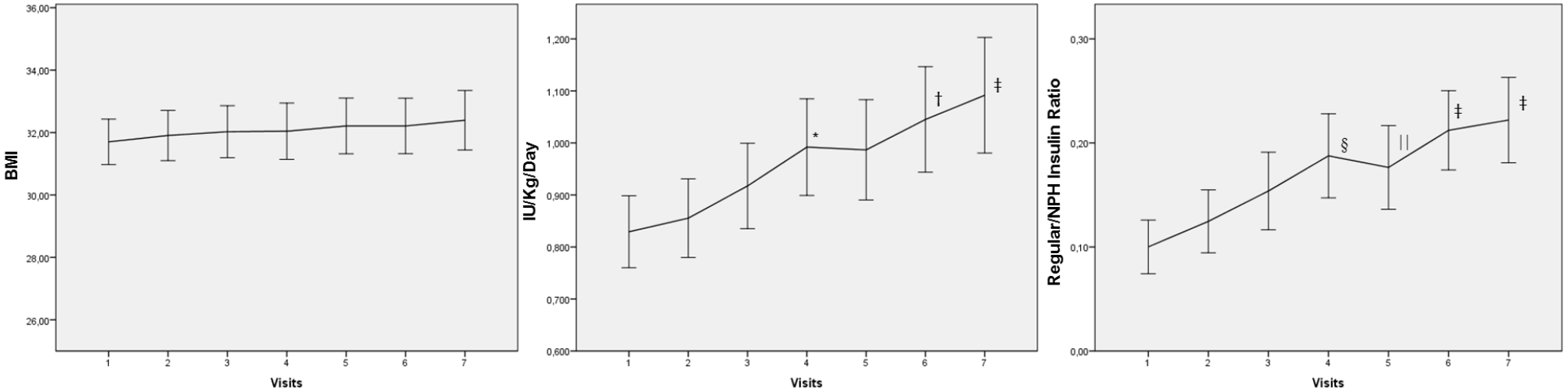

Figure 3. 3A. Body Mass Index *Mean* ± *SE* ; 3B. Daily Prescribed Units of insulin for kilogram of weight *Mean* ± *SE* ; 3C. Daily Prescribed Units of Regular to NPH Insulin Ratio *Mean* ± *SE* *Compared to visit 1 p = 0.005 †Compared to visit 1 p = 0.001 ‡Compared to visit 1 p < 0.001 §Compared to visit 1 p = 0.002 ||Compared to visit 1 p = 0.023

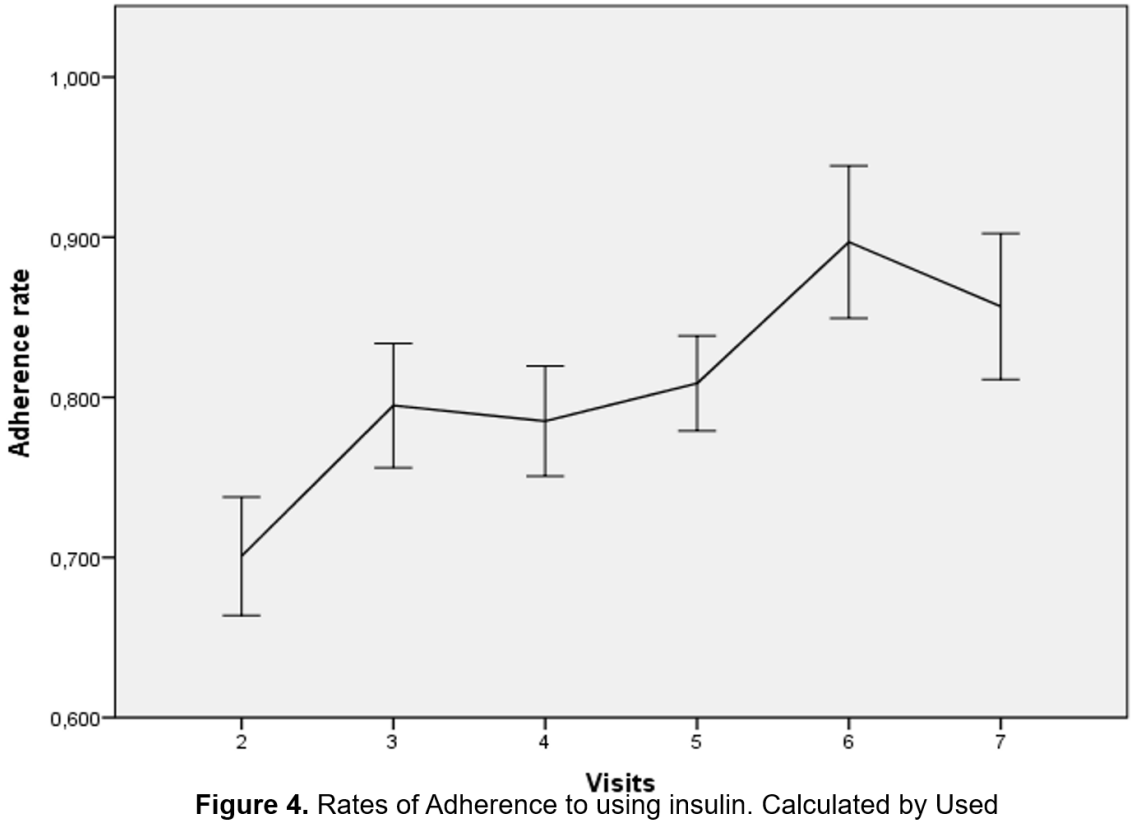

Figure 4. Rates of Adherence to using insulin. Calculated by Used Units/Prescribed Units Ratio *Mean* ± *SE*

ARTIGO 2

Glycemic control in elderly patients with type 2 diabetes and use of pens for insulin application: A Randomized Controlled Clinical Trial.

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Abstract:

Background: Diabetes is a chronic disease with high prevalence in the World and more than 20% of elderly people are affected. Among those who require insulin for treatment, it is necessary strategies to ensure adherence and improved glycemic control. The objective of this study was to evaluate the use of pen devices to help in the application of insulin in this population.

Methods: This is a Randomized Clinical Trial with follow up for 24 weeks. We included 61 patients with type 2 diabetes, 60 years old or more and with Glycated Hemoglobin (HbA1c) greater than or equal to 8.5%. All should be using insulin with syringes or only oral antihyperglicemic agents, but with indication to start insulin. Participants were randomized to receive pens or syringes for insulin delivery. All received lancets and glucometers for blood glucose monitoring.

Results: Mean of HbA1c at baseline was 9.78 ± 1.26% in the “pen group” (PG) and 9.92 ± 1.10% in the “syringe group” (SG). After 24 weeks, PG had lower mean value: 8.06 ± 1.09% vs. 8.95 ± 1.86%, p = 0.027. There was no difference regarding the occurrence of hypoglycemia. Despite the improvement in compliance rates among all patients, there was no difference between groups. When we analyzed Quality of Life, there was deterioration in the scores on the DQOL questionnaire in PG.

Conclusion: The use of pen devices for application of insulin may aid in reducing HbA1c approximately 0.9% during 24 weeks in decompensated elderly patients with Type 2 Diabetes. (clinicaltrial.gov: NCT02517242)

Key Words:

Elderly, Diabetes, Pen Device, Type 2 Diabetes, Glycemic Control.

Introduction:

Diabetes is a disease with high prevalence and incidence, it is estimated that there are 24.1 million of patients with diabetes in the world, and the numbers related to the disease are increasing, it is expected to reach 38.5 million in 2035 (1). In parallel, medical expenses with diabetic patients are high and the costs of patients over 60 years tend to be even higher. Brazil has spent more than 10 million of dollars in 2011, 3 million more than three years earlier (2).

With advancing age, there is a higher prevalence of diabetes (3,4). The risk of disability, fragility, polypharmacy, difficulty with the use of drugs is higher in older subjects (4). All these issues can interfere with the treatment of type 2 diabetes (T2D) in this population.

Patients with high adherence (as example, subjects that use more than 80% of prescribed insulin) have lower costs with health compared to less adherent patients (5). Hospital admissions are related to diabetes by 30-40% among patients older than sixty-five years (6). Despite per-patient pharmacy costs are higher among the most adherents including self-monitoring blood glucose (SMBG) and medicines, it is still necessary to insist on strategies that could improve compliance and to reduce other costs in public health system as financial expenses related to diabetes chronic complications, hospital admissions and visits to the emergency room (5).

In Brazil, metformin, glibenclamide and insulin (NPH and Regular) for diabetes treatment are provided by the public health system (7). Other medications need to be purchased. In clinical practice, for patients that depend of the Public Health System to free distribution of medications, after the start of metformin and nonpharmacological measures, the second oral agent is a sulphonylurea. If glycemic control is not achieved, insulin is started, the most of then is NPH insulin and then the association of regular insulin.

For naïve-insulin elderly patients, the choice of pen devices compared to syringes suggests increase the adherence and persistence on treatment, and it also reduces the occurrence of episodes of hypoglycemia and amount of insulin dose per day (8). Among patients who were already receiving insulin, changing from syringes to pens increased adherence and persistence on treatment; as well reduced the quantity of daily insulin, however, did not reduce episodes of hypoglycemia (8).

Additionally, an important aspect that needs attention is the preference of the patient. According Korytkowski et al (9), 85% of patients believed that pens devices are more discreet for use in public environments, 74% considered easier to use and 85% had more facility to identify the dose to be applied.

Previous studies compared pens and syringes for application of insulin (9-11), used only insulin analogues or premixes, in most cases, these insulins are far from the economic reality of our patients, who have access only to NPH or Regular insulin.

The present study aimed to compare syringes and pen devices on NPH and Regular insulins application among elderly patients with T2D and to observe the glycemic control, all subjects were treated at specialized sector of the public health care in south of Brazil.

Methods:

Study Oversight:

This was a Randomized Clinical Trial to evaluate the use of pens for insulin application over glycemic control among elderly patients with T2D. This study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre and all patients agreed with the Written Informed Consent. Funding was provided by Conselho Nacional de Pesquisa (CNPq) – Brazil and Fundo de Incentivo à Pesquisa

(FIPE) at Hospital de Clínicas de Porto Alegre. This study was registered in clinicaltrial.gov: NCT02517242. Patients are still being enrolled to the study until to full the sample calculated. Here, we presented the partial results.

Study Population:

We selected patients with type 2 diabetes and 60 years old or more, with glycated hemoglobin (HbA1c) greater or equal to 8.5 percent for at least three months in use of insulin with application by syringes or with indication to start insulin use (patients who failed to control diabetes with oral antihyperglycemic treatment provided by Public Health System). Inapt patients to self-administration of insulin, with renal failure (glomerular filtration rate lower than 30 ml/min/1.73m^2 by MDRD) or not agreed to participate were excluded. Patients were selected from outpatients in Diabetes Divison of Hospital de Clínicas de Porto Alegre. Patients were invited to participate from April 2014 to September 2015.

Randomization:

Randomization was done in blocks with giveaway through sealed brown envelopes. The researcher who attended the opening of the envelopes did not know the numerical sequence randomization. The envelopes were opened by the patient. Canditates were randomized to receive pens or syringes for insulin delivery.

Intervention:

Patients of the "pen group" (PG) received insulin pens from brand Luxura®, Eli Lilly. Patient who needed using two types of insulin (basal insulin and rapid insulin), received two pens of different colors of the same brand, as well pen needles. Patients of "syringe group" (SG) received syringes with needles of the same size that the other group. All participants received lancets and blood glucose monitor.

Study Endpoints:

The primary endpoint was the reduction of HbA1c and the difference between these groups. As secondary outcomes, we evaluate the reduction of hypoglycemia and presence of severe, asymptomatic or nocturnal hypoglycemia. Number of medications used, treatment adherence and interference in weight were also evaluated. Quality of life and impact of the disease were assessed by comparing the scores of questionnaires in the first and last visits. We have also evaluated social and cultural profile at baseline. In addition, we evaluated the presence of retinopathy, nephropathy or neuropathy, and cardiovascular and cerebrovascular disease by medical record review.

Study procedures:

Both groups were followed for 24 weeks. Clinical evaluations were made monthly by the same endocrinologist. Patients measured the blood glucose three times a day and filled diary entries. Based on those notes, treatment adjustments were made. To adjust the morning blood glucose, nocturnal NPH insulin was adjust in 4 units, with glucose target between 70 – 130 mg/dl. To adjust blood glucose before lunch, the dose of morning insulin was changed up to 40 units of NPH insulin at this time, and additional alterations were made by increase or reduce in 2 units of insulin Regular, or by beginning 8 units of insulin Regular for patients who did not use rapid-acting insulin. To adjust blood glucose before dinner, adjusting the dose of regular insulin in 2 units before lunch, or NPH insulin before breakfast. If it were necessary starting NPH insulin in the morning, in those patients receiving only bedtime dose without glycemic control throughout the day, the started dose was 12 units.

During each evaluation, patients were questioned about the number of hypoglycemia, presence of severe, asymptomatic and nocturnal hypoglycemia and other adverse effects. We have measured blood pressure in both arms, and twice on each side, after resting in a sitting position, and calculating the mean of these

measurements. We also measured height and weight, and body mass index (kg/m^2) was calculated. The number of medications, antihypertensives, oral antihyperglycemic agents, number of pills and number of insulin injections daily was evaluated every visit.

To evaluate the adherence to the proposed treatment, the patient returned all insulin vials used in the previous months. Patients who used at least eighty percent of the daily insulin prescribed dose in most months were considered as "adherent".

We also evaluated the quality of life and impact of the disease with validated questionnaires in Portuguese. We use DQOL (Diabetes Quality of Life) and BPAID (Problems Areas in Diabetes - Brazil) Questionnaires (12,13). Participants answered both questionnaires at the first and last visits.

Laboratory evaluation:

HbA1c (HPLC ion exchange) was collected before randomization (baseline), and with 12 and 24 weeks during the follow-up.

Statistical analysis:

Sample size was calculated to find a difference between groups of 1% in HbA1c after 24 weeks of follow-up. Thus, for a power of 90% and an alpha error of 5%, we would need to include 56 patients in each group (n = 112). Analyzes were done by intention-to-treat.

Description of variables: Continuous variables with normal distribution are described as mean and standard deviation (SD), variables with non-normal distribution were described as median and interquartile range (P25-75) and categorical variables as number of cases (percentage).

To analyze continuous variables with normal distribution, we used Student t Test. Variables with non-normal distribution were analyzed by Mann-Whitney test. Categorical variables were analyzed using the Chi-Square test. The analysis for

repeated measurements was made by Generalized Estimated Equation with Bonferroni correction. Analyses were done using SPSS 18.0 software (Chicago, IL).

Results:

Study population and treatment:

One hundred and one patients were invited to participate. However, 40 patients did not accept. These subjects had 68.41 years of age, 19.22 years of diabetes and the last HbA1c values were on average 11%. Sixty-one patients were randomized to date, as analyzed their data and statistical power for the primary outcome of this study. Thirty patients were randomized to PG and 31 to SG. Regarding loss following, 8 participants did not complete follow-up, and 7 these subjects were randomized to the SG: 3 participants reported difficulty to going on visits, 3 did not like the group randomized and 2 did not agree to make frequent measurements of blood glucose. Sociodemographic characteristics and medical conditions of both groups are showed in Table 1, and there was no difference between two groups.

Diabetes control:

At 12 weeks of follow-up, this measure was to 8.42 ± 1.27% in the PG and 9.00 ± 1.80% in the SG, with no difference between groups, p = 0.157. At 24 weeks of follow-up, the values were 8.06 ± 1.09% vs. 8.95 ± 1.86% for PG and SG, respectively, p = 0.027. Figure 1 shows these results.

In relation to changing of HbA1c (delta), reduction are significantly higher from baseline to 12 weeks compared with 12 to 24 weeks of follow-up for both groups. In PG, the delta of HbA1c was -1.35 ± 1.69% from baseline to 12 weeks and -0.36 ± 0.83% in 12 to 24 weeks, with difference between this moments (p < 0.001). In SG, the delta of HbA1c was -1.29 ± 2.35% and -0.05 ± 0.95% (p < 0.001) from baseline to 12

weeks and 12 to 24 weeks, respectively. We found no difference in PG delta compared to SG delta from baseline to 12 weeks ($p = 0.53$) and 12 to 24 weeks ($p = 0.18$). Although not statistically significant, the decrement of HbA1c appears to be greater in the PG in relation of SG during 24 weeks of follow up (-1.71 ± 1.71% vs. -1.34 ± 2.32%, $p = 0.48$).

Clinical Outcomes:

We found no difference about number of reported hypoglycemic events by week between the groups, with lower incidence than 0.25 episodes per week in both groups. Additionally, compared to baseline, there was no difference in subsequent months among all patients. There was no difference in the presence of severe, nocturnal or asymptomatic hypoglycemia during the study.

Throughout the study, there was significant improvement of adherence to insulin treatment among all patients. In the second visit, the average adherence was 56.09 ± 39.27%. At 24 weeks of follow-up, this average was 85.26 ± 33.13% ($p < 0.001$). We consider adequate adherence if patients use at least 80% of the prescribed daily doses of insulin. Regardless, there was no difference between the groups.

At the beginning, the dose of insulin [units of insulin per kilogram (IU/Kg)] was similar between groups (PG was 0.64 ± 0.44 IU/Kg and for SG was 0.59 ± 0.44 IU/kg, $p = 0.639$). At the end of follow-up, the PG used 0.89 ± 0.45 IU/Kg and the SG group used 0.65 ± 0.41 IU/Kg ($p = 0.06$).

There was no difference in users of Regular insulin associated with NPH insulin between groups, from baseline to the end of the study. Prior to study inclusion, 26.66% and 22.58% of patients in the PG and SG respectively were receiving Regular insulin ($p = 0.711$). At 24 weeks, 60% and 58.06% of patients in the PG and SG respectively

completed the study using regular insulin (p = 0.404). We found an increasing in the number of "needlesticks" in PG in relation to SG from the fourth month to the end.

In relation to BMI, there was no difference from the beginning to the end of the study, with no difference between groups. Among all patients, BMI was 32.13 ± 0.76 kg/m^2 at baseline and 32.90 ± 0.82 kg/m^2 (p = 1.00) in the final visit. On the first visit, BMI was 31.99 ± 5.59 kg/m^2 and 31.50 ± 5.78 kg/m^2 for PG and SG, respectively (p = 0.480). At the end of follow-up, BMI was 32.80 ± 5.51 kg/m^2 in PG and 33.02 ± 6.42 kg/m^2 in SG (p = 0.897).

We evaluated the number of drugs used during the study. Although we do not find differences over the months among all patients, the SG used less medication. PG used 8.14 ± 2.4 drugs while SG used 7.20 ± 2.09 drugs at baseline (p = 0.11). At the last evaluation, PG used 8.74 ± 2.50 drugs while SG used 7.17 ± 2.04 drugs (p = 0.02). Despite this statistic, clinically this value can not be appreciated because there was no difference between the use of referred tablets in daily, number of antihypertensive or antihyperglycemic agents.

To assess the Quality of Life, BPAID questionnaire shows no points deemed appropriate cuts, and our analysis was comparative between the first and last visit. SG scored 75.06 ± 22.77 while PG scored 86.60 ± 25.87 points on the first visit (p = 0.065). At the last visit, there was worst performance of the PG group (73.33 ± 32.15 vs. 54.93 ± 37.96, p = 0.046). The higher the score, the worse the quality of life in relation to diabetes. In the questionnaire DQOL, we use variables "impact of disease" and "satisfaction" with the treatment. Other validity variables in this survey do not apply to this population. PG reported a higher “impact of the disease” on their lives, but this difference was already found in the first evaluation. No differences between the groups on the question "satisfaction".

Discussion:

In this RCT, pen devices for applying insulin among elderly patients with T2D had superior results in comparison to syringes. At 24 weeks, PG had lower values for HbA1c.

Incidence of hypoglycemia was low. Evaluation of gravity, occurrence of asymptomatic or nocturnal episodes became impaired for this reason. Among those who reported hypoglycemia, most had less than two episodes per month. This low frequency influenced the final median. Possibly the small number of hypoglycemia was due to the high levels of glycated hemoglobin found at baseline in all group of patients.

Despite the significant reduction over 24 weeks, yet the final HbA1c was above of recommended, especially in SG. Considering that our patients were elderly, with high rates of complications, the strict glucose control could bring greater losses and risks (14,15).

The occurrence of hypoglycemia is less frequent among patients with T2D compared to type 1 diabetes (16). However, these events are not negligible, and with advancing age, the incidence of hypoglycemia appears to increase, regardless of glycemic control (16). In relation to intensive diabetes treatment, the risk of hypoglycemia tends to increase.

Regarding adherence to treatment, we achieved adherence levels similar to studies already conducted, regardless of the application method. Using insulin for a long period can improve adherence, particularly among the elderly (5,10,17). Needing to return the refills used each visit may have influenced this result. In addition, all patients received technical of application guidance and revised the dose used with the equipment (syringe or pen).

Insulin treatment was becoming more intense throughout the study, proof that the IU/kg has increased during the follow-up. More patients started using Regular insulin in both groups. There was no difference between groups, confirming the commitment of researchers to treat all patients, regardless of group, aiming to better glycemic control.

Our main limitation is the difficulty of blinding. Despite the improvement in HbA1c in both groups and the use of protocols to adjust the insulin dose, the researcher may have been influenced by the group of patient belongs at the time of evaluation. Another limitation is the difficulty that some patients faced to make SMBG with visual or cognitive difficulties. In some cases, adjustment of treatment turned out to be delayed for this reason. Regarding the use of pens, some patients requested help to a family member at the beginning of the intervention. Nevertheless, we evaluated the degree of dependence and it was not different between groups.

Faced with few options free in Public health system of diabetes treatment in Brazil, measures to improve adherence to treatment must be instituted. We believe that using of insulin in chronically decompensated patients may help improve glycemic control. In addition, use of pens to application insulin can be one of them. As many patients, even before the possibility of starting the use of a third drug orally, for financial reasons already need to use insulin.

In conclusion, the presented data showed that the use of pens to apply insulin could help in reducing HbA1c alone, independent of other strategies to improve adherence, in elderly T2D patients.

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Disclosure:

All authors have no conflict of interest to declare.

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TABLE 1:

Table1. Baseline Characteristics of the Study Population			
	Pen Group	**Syringe Group**	**(p value)**
Age in years *(mean* ± SD)	66.70 ± 5.32	66.48 ± 4.88	0.869
Male sex (%)	40.0	32.3	0.529
Race (%)			0.954
White	70.0	67.7	
Black	13.3	16.1	
Other	16.7	16.1	
Religion (%)			0.250
Catolics	73.3	61.3	
Evangelics	16.7	19.4	
Spiritualists	6.70	3.20	
Others	3.30	16.2	
Family Income (%)*			0.224
up to 1 minimum wage	13.4	19.4	
1-2 minimum wages	43.3	58.1	
over 2 minimum wages	42.3	22.6	
Years of education in years (%)			0.355
uneducated or less than 1 year	6.70	12.9	
1 to 3 years	3.30	12.9	
4 to 8 years	50.0	48.4	
9 years or more	40.0	25.8	
History of smoking (%)			0.732
Never smoking	66.7	61.3	
current smoking	3.30	3.20	
Former	30.0	35.2	
Alcohol consumption (%)			0.769
Never drinking	43.3	45.2	
Social Considers	40.0	38.7	
Alcohol abusers	3.30	16.1	
Former	13.3	-	
Diabetic Retinopathy† (%)			0.803
Absent	11/23 (47.83)	14/23 (60.87)	
Mild or moderative Non proliferative	07/23 (30.43)	06/23 (26.87)	
Severe Non proliferative	01/23 (04.35)	00/23 (-)	
Proliferative	04/23 (17.39)	03/23 (13.04)	
Diabetic Nefropathy‡ (%)			0.154
Absent	12/24 (50.00)	11/30 (36.67)	
Albuminuria increased	07/24 (29.17)	12/30 (40.00)	
Albuminuria greatly increased	05/24 (20.83)	07/30 (23.33)	
Nefrotic Albuminuria	00/24 (-)	00/30 (-)	
Diabetic Neuropathy‡ (%)			0.738
Absent	14/24 (58.33)	16/26 (61.54)	
Present	10/24 (41.67)	10/26 (38.46)	
Presence of CVD § n and (%)	07/28 (24.13)	08/31 (25.81)	0.585
Presence of ischemic cardiopathy|| n and (%)	05/28 (17.85)	04/31 (12.90)	0.572
Time of Diabetes in years (median ± IQ)	20 (IQ 10.75-25.25)	13 (IQ 10.00-23.50)	0.146
Time using insulin in years (median ± IQ)	10 (IQ 3.75-16.25)	5 (IQ 2.00-13.00)	0.099
Glycated hemoglobin (mean ±SD)	9.78% ± 1.26	9.93% ± 1.10	0.617
Positive familiar history for Diabetes (%)	66.6	70.97	0.547
Presence of Hypertension (%)	96.7	83.87	0.229
Number of antihyperglycemic agents *(median* ± IQ*)*	1 (IQ 1.00-1.50)	1 (IQ 1.00-2.00)	0.119
Classes of antihyperglycemic users (%)			0.088
None	02/30 (06.66)	04/31 (12.90)	
Metformin	21/30 (70.00)	13/31 (41.93)	

Metformin and Glibenclamide	07/30 (23.33)	14/31 (45.16)	
Time of Hypertension in years (mean ±SD)	17.36 ± 9.38	14.64 ± 9.08	0.271
Number of use medicins (mean ±SD)	8.14 ± 2.40	7.02 ± 2.09	0.115
Number of antihypertensive (median ± IQ)	3 (IQ 2.00-4.00)	3 (IQ 2.00-3.00)	0.153
Number of use tablet (mean ±SD)	14.16 ± 4.80	12.77 ± 5.20	0.295
Insulin dose per kg / day (mean ±SD)	0.64 ± 0.44	0.59 ± 0.44	0.639
BMI (kg/m^2) (mean ±SD)	31.99 ± 5.59	31.50 ± 5.78	0.480
Systolic blood pressure in mm Hg (median ± IQ)	140 (IQ 127.5-150.0)	130 (IQ 120.0-150.0)	0.193
Diastolic blood pressure in mm Hg (median ±IQ)	80 (IQ 67.50-89.25)	72 (IQ 60.00-84.00)	0.329

*minimun wage iqual to $ 220,70 (reference year = august/2015)

†chart review

‡chart review; we consider albuminuria >14mg/g of Creatinine (albuminuria increased) and >140 mg/g of Creatinine (albuminuria greatly increased), and neuropathy to patients with description of positive monofilament test, sensorial changes or suggestive lesions.
§ Cerebrovascular disease (CVD) history of transient ischemic attack or stroke.
||history of unstable angina, acute myocardial infarction or diagnosis of ischemic heart disease

FIGURE:

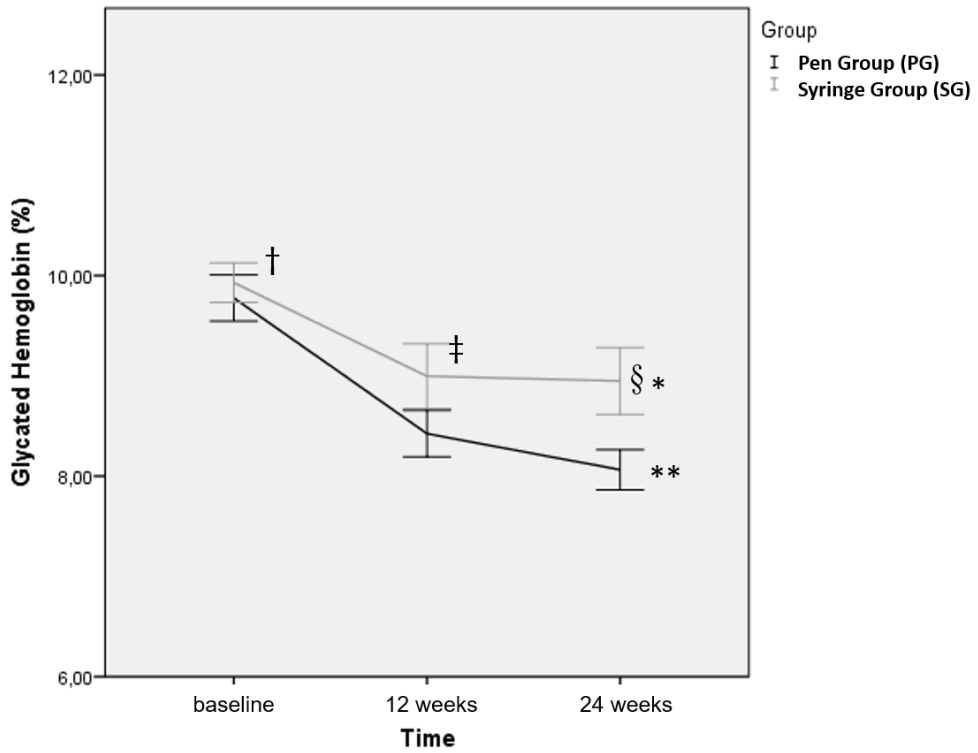

Figure 1. Glycated Hemoglobin (HbA1c). *Mean ± SD.* † *Compare PG with SG at baseline, p = 0.617.* ‡ *Compare HbA1c between groups in 12 weeks, p = 0.157. Delta of HbA1c at baseline to 12 weeks: PG vs. SG, p = 0.53.* § *Compare HbA1c between groups in 24 weeks, p = 0.027. Delta of HbA1c at 12 to 24 weeks: PG vs. SG, p = 0.18; and Delta of HbA1c at baseline to 24 weeks: PG vs. SG, p = 0.48. * In SG: Compare 12 weeks with baseline, p = 0.001; Compare 24 weeks with baseline, p = 0.001; and Compare 24 weeks with 12 weeks, p = 0.708. ** In PG: Compare 12 weeks with baseline, p < 0.001; Compare 24 weeks with baseline, p < 0.001; and Compare 24 weeks with 12 weeks, p = 0.025.*

ARTIGO 3

Self-Monitoring Blood Glucose improves glycemic control among patients with Type 2 Diabetes without intensive treatment: a systematic review and meta-analysis of Randomized Clinical Trials.

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Abstract:

Background: The role of the Self-Monitoring of Blood Glucose (SMBG) in the treatment of patients with type 2 diabetes (T2D) is still unclear. Previous systematic reviews and meta-analysis have conflicting results and even Clinical Trials were conducted with different methodologies.

Objectives: to evaluate the effect of SMBG on glycemic control in patients with T2D with conventional treatment (included patients with no intensive treatment with insulin).

Methods: We selected Randomized Controlled Trials (RCTs) in Medline (via Pubmed), Embase and Cochrane Central databases up to January 21st at 2016. Two independent reviewers assessed the eligibility of references. Selected studies were reviewed in full-text. We included RCTs conducted in patients with T2D that evaluated SMBG compared to a control group. Assessment of quality was performed by two independent reviewers. The effects of SMBG on glycated hemoglobin were accessed by direct meta-analyses with Weighted mean difference in 12, 24 weeks and 1 year.

Results: When compared to control group, SMBG was associated with reduced glycated hemoglobin (HbA1c) in 12 weeks (-0.31%; 95% CI: -0.57 to -0.05) and 24 weeks (-0.34%; 95%CI: -0.52 to -0.17), with no difference for 1 year. Subgroup analysis including studies with HbA1c at baseline greater than HbA1c 8% showed a higher benefit on reduction of HbA1c: (-0.83%; 95% CI: -1.55 to -0.11) at 12 weeks and (-0.48%; 95% CI: -0.77 to -0.19) at 24 weeks. There was no difference in one-year.

Limitations: great variability of RCTs´ methods.

Conclusion: The use of SMBG by patients with T2D without intensive treatment seems to lead to better glycemic control in the short term. Especially chronically decompensated patients presented higher benefit of this intervention.

PROSPERO register: CRD42016033558.

Key Words:

Type 2 Diabetes, SMBG, Self-Monitoring of Blood Glucose, Glycemic Control.

Introduction:

Following the natural history of disease in patients with type 2 diabetes (T2D), the treatment begins with lifestyle change and then with the addition of one or more classes of oral antihyperglycemic agents, and finally insulin is added to the treatment (1). Parallel to this clinical development, glycemic control is performed by measuring the glycated hemoglobin (HbA1c). However, blood glucose may also reflect the glycemic control of the patient, and self-monitoring of blood glucose (SMBG) may have a reducing effect of HbA1c like the addition of a drug (1). Nevertheless, the most appropriate way to prescribe SMBG for patients with T2D is still controversial, especially in subjects that use only oral medications or insulin without an intensive treatment.

Some Meta-analyzes (2-7) tried to show these effects. However, the results are conflicting and inconclusive, and they did not include patients on insulin treatment (2).

Curiously, the number of blood glucose measurements is not established in literature, and in clinical practice, each physician has a different prescription. Some authors suggest conducting more frequently SMBG. Lu *et al* (8) suggest conducting at least two pre-prandial measurements per day. Davidson *et al* (9) suggests, in addition to pre-prandial evaluation, also advice postprandial measurements. Schnell *et al* (10) requested measures only in the two days preceding the medical evaluations. Additionally, Bonomo *et al* (11) and Chidum *el al* (12) requested only three measures distributed throughout the week. In contrast, Swedes *et al* (14) suggested conduct more intensive measures (six times a day), but only twice a week. All these authors studied T2D patients only on oral medications.

A Brazilian Cross Sectional Study (15) evaluated patients followed in the public health system in five regions of Brazil. In this study, patients who reported performing SMBG at least once a day showed better glycemic control than patients who did not

perform these measures. In the interim, the HbA1c was higher than desired in both groups (9.3 ± 2.1% vs. 9.7 ± 2.3%, p = 0.008).

Costs of SMBG also need to be considered. Routine measurement of blood glucose in patients with newly diagnosed T2D can increase the monthly costs of the disease in 81% (16). For patients with diagnosis at long time, the cost impact will depend of the treatment used for diabetes. Among patients with only one oral antihyperglycemic agent, the costs of SMBG reach 84.5% of the total cost for all diabetes treatment, while among patients with intensive treatment of insulin analogues, the costs of SMBG are around 46.9% of all treatment (17). Thus, the real benefit of this strategy needs to be evaluated to confirm the necessity to perform blood glucose and to define the correct prescription of SMBG for different types of treatments of the diabetes.

Our objective was defining the benefit of SMBG for glycemic control among patients with T2D, users or not of insulin without intensive treatment of diabetes.

Methods:

Protocol and Registration:

This systematic review and meta-analysis follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (18) statement and it is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (19) – CRD42016033558.

Study searches and selection:

We searched all randomized clinical trials (RCTs) in Medline (via Pubmed), Embase, Cochrane Central databases, ClinicalTrials.gov and abstracts in the journals of the American Diabetes Association and the European Association for the Study of

Diabetes published until January 21 at 2016. We restricted to idioms English and Spanish.

The terms used on searches were: (randomized controlled trial) [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract]) AND "Diabetes Mellitus, Type 2" [Mesh] AND "Blood Glucose Self-Monitoring" [Mesh] with validated filters to RCTs (20).

Two researchers (RVM and DVR) independently reviewed the references for eligible studies; discordances were solved by consensus. We included RCTs conducted in patients with T2D that had evaluated some SMBG compared to a control group (with no measurement, with standard care or only urinary glucose monitoring). We excluded studies that evaluated Continuous Monitoring of Blood Glucose and that SMBG was present in both groups with frequency of measurements higher than once a week in each group or SMBG was part of a more complex intervention (such as education). Studies not reporting glycemic control outcomes were also excluded. All potentially eligible trials were considered for review, regardless of the primary outcome. The treatment used for diabetes was not taken into consideration, except studies with patients on intensive treatment of insulin [using basal insulin (human or long analog insulin) and rapid action insulin (regular or ultra-rapid action analogs)] were excluded.

Quality assessment:

Quality of the included studies was evaluated with the Cochrane Collaboration tool for risk of bias (21, 22). We evaluated the six suggested topics: random sequence generation; allocation concealment; blinding; incomplete outcome data; selective reporting. For other biases, the source of funding was assessed.

Data extraction:

The following data were extracted from the included studies: age, gender, time of diabetes, the treatment administered, prior performing SMBG or not, weight and body mass index. We also evaluated the frequency of glucose monitoring and method employed in each group, associated interventions, and HbA1c.

The control group was composed for no SMBG; however, in two studies (11, 23) the control group had one measurement a week. In the studies that had three different groups (8, 24-27), we considered as control group the group with no SMBG and the comparison group, that with some type of SMBG. In addition, the third group was disregarded for this meta-analysis. In two studied, this third group had other type of urinary measurements (8, 24). One study had this group had palm sticks (25). Other study this third group had adjustment of physical activity and diet based on these results (26), and the last study (27) had web based monitoring system only this third group.

Our main outcome was the glycemic control in the SMBG in comparison to control groups assessed by the mean of the post-intervention HbA1c.

Statistical analysis:

HbA1c was extracted as mean and standard deviation (SD). In studies with standard error (SE), SD was calculated. We used direct meta-analysis to compare the intervention group with the control group. We planned some stratified analyses by follow-up length (12 and 24 weeks and 1 year) and type of comparator (no intervention or less intensive monitoring). We did a subgroup analysis in relation to glycemic control at baseline (studies were divided between HbA1c lower or equal than 8%, and higher than 8%). Evaluation of heterogeneity among studies accomplished by I-square test (I^2). Random effects model was used to meta-analysis (28, 29). We made subgroups analysis and meta-regression of continuous values to explain the heterogeneity. We also performed trial sequential analysis (TSA) to assess if the available data definitively

confirm or discard a difference of at least 0.4% in HbA1c between treatment and control groups. We performed the analyses in Stata version 12.0 (Stata Inc., College Station, Texas, USA) and the TSA with TSA software version 0.9 (beta) (Copenhagen Trial Unit). RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark) was also used to create risk of bias figures.

Results:

We identified 707 abstracts, however 358 were in duplicate and were excluded by the titles. In total, 349 abstracts were evaluated. These, 294 out of 358, were not referred to RCTs, T2D, or SMBG. Therefore, 55 references were selected to analyses of the full text. Thirty-three studies were excluded: 24 were repeated, four approached another issue, one study was in another language (unknown to the authors), two studies did not describe the intervention and other two the full text was not available, although of the insistent contact to the authors. Therefore, 22 articles would be included in this meta-analysis. Study flow diagram is presented in Figure 1.

We have included 4338 patients in this meta-analysis. The average age was 59 years, with no difference between the two groups evaluated. Regarding the time of diagnosis of diabetes, the average in years was 6.96 vs. 7.22, and for Body Mass Index (BMI), the average was 30.68 kg/m^2 vs. 30.21 kg/m^2, respectively for intervention group and the control group for both variables and with no difference between groups.

Description of studies:

Eighteen studies compared SMBG to no intervention (8-10, 12-14, 24-27, 30-37). Two studies used monitoring of urinary glucose (38, 39) and other two studies used SMBG with lower intensity (one time per week only) as control (11,23). There was great variation in the frequency of blood glucose measurements among studies. Only

12 studies conducted at least seven tests of blood glucose per week according protocols, in different moment of the day with no standard period (8, 9, 13, 14, 25, 27, 30, 33, 34, 36, 37, 39)**.** Some studies preferred various measurements throughout the day, few days per week. Other studies were shipping measures blood glucose levels over the days of the week. Only four studies included users of insulin. Detailed description of studies' characteristics is presented in Table 1 and patient's characteristics are presented in Table 2. Quality of included studies is shown in Table 3 and Figure 2.

Fourteen studies described treatment for diabetes, at baseline, with no difference between the arms of these studies. Regarding the use of oral anti-hyperglycemic agents, the frequency of use ranged from 65.2% to 85% in the intervention group and 56% to 85% in the control group. According to the number of used classes, monotherapy ranged from 8% to 69.9% in the intervention group and 7% to 71% in the control group. For combined therapy (more than one drug), the frequency ranged from 1% to 27% in the intervention group and 2% to 33% in the control group. In relation of classes used, only 9 studies have discriminated. The use of metformin ranged from 18.4 to 76% in the intervention group and 12 to 79% in the control group. Sulfonylureas were used in 23 to 69.9% in the intervention group and 14 to 71.7% in the control group. Other classes of antihyperglycemic agents were used from 9 to 10.9% in the intervention group and 7 to 30% in the control group.

Four studies included patients using insulin (13, 27, 32, 35). Only one study (35) included only patients using insulin. It was used long action insulins at bedtime or pre-mixtures. Other study (27) had 24% of insulin users in each group, in contrast with the third (13) that had only 3% and 1% of insulin users in the intervention group and control group, respectively, and none of them described the type or doses of insulin. The last study no records the proportion of patients using insulin in the sample (32).

Glycemic control:

At baseline, the mean HbA1c was 8.22% in the intervention group and 8.11% in the control group. At 12 weeks, the group with SMBG was associated with better glycemic control than control group: reduction of HbA1c (-0.31%; 95% CI: -0.57 to -0.05). Eleven studies were used to this analysis with 1273 patients in intervention group and 1285 patients in control group. At 24 weeks, there was also better glycemic control with SMBG group: reduction of HbA1c (-0.34%; 95% CI: -0.52 to -0.17). Nineteen studies contributed to this analysis with 2131 patients in intervention group and 2207 in the control group. In both analyses, high heterogeneity was found. Results are presented on Figures 3 and 4.

With longer follow-up (one year), no difference was found between experimental and control groups: reduction of HbA1c (-0.02%; 95% CI: -0.17 to 0.13) with high heterogeneity in analysis. Eight studies contributed to one-year analysis, and at this moment, there were 947 patients in the intervention group and 977 in the control group. Results are presented on Figure 5.

In relation to glycemic control at baseline, the additional analysis including only studies with HbA1c higher than 8% showed positive results in favor of SMBG – decrease of HbA1c (-0.83%; 95% CI: -1.55 to -0.11) at 12 weeks and (-0.48%; 95% CI: -0.77 to -0.19) at 24 weeks. There was no difference in one-year: (-0.11%; 95% CI: -0.42 to 0.21). For studies with HbA1c lower or equal to 8% at baseline, there was reduction only at 24 weeks (-0.20%; 95% CI: -0.37 to -0.03), with no difference at 12 weeks (-0.06%; 95% CI: -0.19 to 0.07) or in one year (0.04%; 95% CI: -0.08 to 0.16). There were low heterogeneity in one-year and moderate heterogeneity in 12 and 24 weeks when isolate analysis was done to HbA1c lower or equal to 8%. These analysis are showed in Figures 6, 7 and 8.

Meta-regression was performed with baseline HbA1c values. In 12 and 24 weeks, this analysis could not explain the heterogeneity (p = 0.31). But in one year of follow-up, there was linear association (p = 0.042) with residual heterogeneity of 18.1%. Bubble plot in Figure 9.

Subanalysis was also made in relation to number of tests performed per week. There were reduction of HbA1c when analyzed studies with upto seven measurements per week for 12 weeks (-0.48%; 95% CI: -0.93 to -0.03) and 24 weeks (-0.30%; 95% CI: -0.40 to -0.20). Among studies with more than 7 tests/week, there were reduction in 12 weeks (-0.16%; 95% CI: -0.29 to -0.02) and 24 weeks (-0.54%; 95% CI: -0.90 to -0.17). At one-year follow up, there was no difference, regardless of the subanalysis for number of tests [(-0.04%; 95% CI: -0.22 to 0.14) to up to 7 tests/week and (-0.05%; 95% CI: -0.20 to 0.10) to more than 7 test/week]. Heterogeneity becomes low when only studies with more tests remains in analysis. Analyse were presented in Figures 10, 11 and 12.

Trial Sequential Analysis:

As presented in figures 13, 14 and 15, we performed TSA for 12, 24 weeks and 1 year in relation of all studies in association. At 12 weeks of follow-up, no secure conclusions are allowed, as the Z-curve did not cross any of the boundaries nor reached the optimal sample size. At 24 weeks, Z-curve crosses the upper boundary, so confirming that SMBG lowers HbA1c of at least 0.4%. At last, in the one-year analysis, no difference was found and the Z-curve crossed the futility boundary and reached the optimal sample size, so a difference of at least 0.4% was definitively discarded.

Discussion:

This meta-analysis of RCTs shows a benefit of SMBG for glycemic control in short term at 12 and 24 weeks, this improvement is not remained in long term.

There is disparity on the frequency of performing SMBG among studies, which may explain the conflicting results between 24 weeks and one year follow-up. The studies that were included in the final analysis had a lower frequency of blood glucose measurements, compared to the larger number of studies with performing SMBG with more than seven sticks a week at 24 weeks of follow-up. On the other hand, Schnell *et al* was the study with the highest weight in the meta-analysis with random effects in one year, with individual results in favor of SMBG. This study performed SMBG only three days before the medical visits and, in generally, only every three months. Furthermore, the HbA1c at baseline was the highest (around 8.9%) among the studies in this analysis (10).

In this sense, the effect of SMBG may be influenced by the initial values of the HbA1c. Considering the individual results of the studies in favor of SMBG at 12 and 24 weeks, patients with HbA1c higher than 8% had the best results with important reduction (-0.83% and -0.48%, respectively). Therefore, our results in subgroup analysis suggested that the effect on SMBG on glycemic control may be more important among the chronically decompensated patients. In the analysis in one year, only three studies had HbA1c greater than 8.0% (10, 36, 38) and maybe can justify the negative effect of the SMBG at this time, in compassion at 24 weeks that 11 out of 19 studies had HbA1c higher than 8%. Strengthening our results, that the initial control glycemic is very important, Chidum *et al* (12) presented the greater reduction in favor of intervention group in our study. The HbA1c at baseline was higher in the intervention group (9.6% vs. 8.5%, $p < 0.05$), although the control group was also much

decompensated. In contrast, in all other studies the HbA1c was similar between the groups at baseline.

Regarding the use of insulin, Nauck *et al* (35) developed the experiment with insulin users only. There are no other studies with this characteristic. In this study, patients in the intervention group performed only four blood glucose measurements per week, all on the same day. There was no difference in HbA1c values at 12 and 24 weeks and one year. However, both groups had low values of HbA1c at baseline (7.3% vs. 7.3%, p = 0.80) in compare with other studies and, in general, patients used insulin in low doses (insulin of long acting in bedtime or pre-mixtures) (35). Ismail *et al* (32) found more reduction of HbA1c in the intervention group compared to the control group (delta: -0.4% vs. 0.9%, p = 0.001). In this paper, the number of capillary measurements was variable, with average of 2.8 per week. The HbA1c levels were also higher than in other studies (9.2% vs. 8.9% in intervention and control group, respectively). However, there is no record of the proportion of patients using insulin in the sample. In the other two studies, Lim *et al* (27) had 24% of insulin users in each group and Zhang *et al* (13) had 3% and 1% of insulin users in the intervention group and control group, respectively, and none of them describes type or doses of insulin. With these data, we can not conclude whether there is difference in relation to glycemic control with performing SMBG for these insulin users.

The additional TSA strengthens the previously described findings. This method combines the temporal information, putting in publication sequence, the included studies. The Z curve represents the sum of the results to date. To exceed the significance boundaries, either higher or lower, it brings the information that there is no need to include new studies for the same intervention. If reaching the maximum significance "n" within the confidence interval, we can accept the null hypothesis with safety, also no need to include new studies (28, 29).

This meta-analysis was the one that included the largest number of studies compared to other available in the literature. The most recent meta-analysis was published in 2012 (7). Despite it has been performed with individual data, just six RCTs were included. The authors limited selection of studies from 2000 to 2010. Reducing HbA1c was -0.18%, -0.25% and -0.23% at 12 and 24 weeks and 1 year, respectively, in favor to SMBG (7). Although statistically significant, these values have not clinical relevance. After 2010, at least 14 studies have been published. Clar *et al* (2) synthesized the meta-analysis performed on SMBG in patients with T2D prior to 2010 in a systematic review, and the results were divergent.

Our limitations were the differences in frequency of blood glucose measurements, inherent to evaluate studies, and there was no possibility of joining them to determine the best number of weekly measures. In addition, we gathered in the control group studies without any action with studies performed urinary glucose monitoring or even SMBG measures to a lesser frequency. However, Jansen *et al* (40) and Welschen *et al* (41), had already made these subgroup analyzes, compared SMBG with Self-Monitoring of Urinary Glucose (SMUG), with no difference in reducing HbA1c. We have included two studies (38, 39) that used SMUG as control. These studies showed neutral results for glycemic control in their individual analysis and may have influenced in favor of the control group. This is the first meta-analysis that included patients taking insulin.

The high heterogeneity found in all analyzes can be due to the large number of small studies that participated in our sample, with different methodologies and great variations in results. In one-year, heterogeneity can be explained for values of HbA1c at baseline.

In conclusion, performing SMBG seems to help in glycemic control temporarily among patients with T2D, especially in patients with HbA1c higher than 8%. Chronically decompensated patients seem to have more benefits of this strategy.

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Disclosure:

All authors have no conflict of interest to declare.

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TABLES:

Table 1. Characteristcs of studies.

Studies	Frequency at SMBG in Intervention Group	Frequency at SMBG or other intervention in Control Group*	Duration of intervention	Setting	Nº of participants	Nº of visits for each participant	Timing of visits	Inclusion of insulin users
Allen et al 1990	9/week	9 testing urine glucose per week	6 months	General medical and triage clinics of the Durham Veterans Administration Medical Center, USA.	61	3	At months 0, 3 and 6	No
Barnett et al 2008	10/week	None	27 weeks	133 specialist centres in seven countries (Czech Republic, Hungary, Iran, Malaysia, Poland, Slovakia and Turkey).	610	7	At weeks -2,0,3,6,9,18, 27	No
Bonomo et al 2010	3/week	1/week	6 months	Diabetes Clinic at the San Luigi Gonzaga University Hospital in Orbassano, Italy.	273	3	At months 0,3 and 6	No
Chidum et al 2011	3/week	None	6 months	Primary care clinics from Trinidad and Tobago	61	3	At months 0,3 and 6	No
Dallosso et al 2014	not frequency described of SMBG	not frequency described of urine testing	18 months	General practices in England	292	4	At months 0,6,12 and 18	No
Davidson et al 2005	36/week	None	6 months	Clinic community of USA.	89	5 with dietitian, number with nurse not specified	At weeks 0,2,4,8 and 12 with dietitan, those with nurse not specified	No

Farmer et al 2007	6/week	None	12 months	Department of Primary Health Care, University of Oxford, USA.	453	6	At months 0,1,3,6,9 and 12	No
Guerci et al 2003	6/week	None	6 months	Multicentre study conducted in hospitals in France.	689	4	At weeks 0,6,12 and 24	No
Harashima et al 2013	9/week	None	6 months	Outpatients of Kyoto University hospital were recruited, Japan.	137	5	At weeks 0,6, 12, 18 and 24.	No
Ismail et al 2013	2,8/week	None	6 months	Two health clinics located in Negeri Sembilan, and at three others in Selangor, Malaysia.	105	7 with nurse and 4 with a doctor	At months 0,1,2,3,4,5 and 6 with nurse and at months 0,2,4 and 6 with a doctor	Yes
Kempf et al 2013	7/week	None	12 weeks of intervention and follow-up until 18 months	Bulgarian clinic.	124	3	At weeks 0 and 12 and at month 18	No
Kleefstra et al 2010	8/week	None	12 months	Netherlands.	41	5	At months 0,3,6,9 and 12	No
Lim et al 2011	8/week	None	6 months	Clinic of the Seoul National University Bundang Hospital, South Korea.	154	2	At months 0 and 6	Yes
Lu et al 2011	16/week	None	6 months	Two Diabetes Centers at China.	108	7	At months 0,1,2,3,4,5 and 6	No
Malanda et al 2015	6/week	None	12 months	University Medical Center, Amsterdam, Netherlands.	181	3	At months 0, 4 and 12	No
Nauck et al 2014	4/week	None	12 months	Various clinical centers at Germany.	300	5	At months 0,3,6,9 and 12	Yes**

O´Kane et al 2010	8/week	None	12 months	Diabetes services at Altnagelvin, Belfast City, Causeway, and the Ulster Hospitals, Northern Ireland.	184	5	At months 0,3,6,9,12	No
Scherbaum et al 2008	4/week	1/week	12 months	Six institutions from Germany.	202	4	At months 0,3,6 and 12	No
Schnell et al 2013	7x/day in three days before each medical evaluation.	None	12 months	34 primary care practices across the eastern U.S.	481	6	At months 0,1,3,6,9 and 12	No
Schwedes et al 2002	12/week	None	6 months	21 centers in Germany and Austria.	223	8 and 4 with a nurse with a questionnaire	A visit each 4 weeks and nurse visit at weeks 0, 4,12 and 20	No
Shiraiwa et al 2010	10/week	None	4 months	General hospital from Japan.	71	3	At months 0,2 and 4	No
Zhang et al 2012	14/week	None	6 months	Dartmouth College, Hanover, New Hampshire; Stanford Medical Center, Stanford, California; and Pacific Endocrine Diabetes Health Center, San Jose, California.	169	3	At months 0,1 and 6	Yes

* Reference to the group used as control for this meta-analysis. Studies with three different groups, we only use the group without intervention or minimal intervention for comparison. Potential interventions in both groups were not considered for the description of this table.

** Nauck at al included patients with T2DM that use insulin only.

Table 2. Characteristics of patients at baseline

Author, Year		n	Women (%)	Mean age (years)	Meas Diabetes duration (years)	Mean HbA1c (%)	BMI (Kg/m^2)
Allen et al 1990	**IG**	27	*	58.2	6.80	12.4	*
	CG	27	*	58.9	9.00	11.7	*
Barnet et al 2008	**IG**	311	50.48	55.9	2.80	8.12	30.5
	CG	299	47.82	56.1	2.80	8.12	30.3
Bonomo et al 2010	**IG**	96	71.87	65.3	10.76	8.06	28.85
	CG	117	20.90	62.8	10.38	8.04	29.13
Chidum et al 2011	**IG**	30	73.30	60.1	7.70	9.6	30.5
	CG	31	83.87	59.4	7.80	8.4	30.9
Dallosso et al 2014	**IG**	140	49.28	57.1	**	8.1	34.2
	CG	152	42.76	59.4	**	8.2	32.8
Davidson et al 2005	**IG**	43	79.06	50.9	5.80	8.5	33.4
	CG	45	68.88	49.8	5.50	8.4	31.7
Farmer et al 2007	**IG**	150	41.33	65.2	3.00	7.41	31.9
	CG	152	44.07	66.3	3.00	7.49	30.9
Guerci et al 2003	**IG**	345	46.37	60.9	7.69	9.0	30.4
	CG	344	43.31	62.2	8.40	8.9	29.7
Harashima et al 2013	**IG**	46	43.47	64.3	8.50	7.44	*
	CG	45	42.22	63.1	8.40	7.46	*
Ismail et al 2013	**IG**	58	53.44	54.0	6.33	9.2	27.2
	CG	47	68.08	52.7	6.59	8.9	27.7
Kempf et al 2013	**IG**	63	*	56.0	3.00	7.4	30.8
	CG	61	*	58.9	3.80	7.5	30.6
Kleefstra et al 2010	**IG**	22	45.45	59.5	5.00	7.6	32.7
	CG	19	26.31	58.7	8.00	7.7	29.0
Lim et al 2011	**IG**	51	54.90	67.2	15.40	7.9	24.9
	CG	52	59.61	68.1	15.80	7.9	25.4
Lu et al 2011	**IG**	35	42.85	53.03	4.00	8.5	24.67
	CG	35	34.28	57.26	3.00	8.6	25.45
Malanda et al 2015	**IG**	60	28.33	60.8	6.00	7.5	31.8
	CG	62	32.25	61.2	7.00	7.4	31.7
Nauck et al 2014	**IG**	151	34.43	65.0	12.0	7.3	30.0
	CG	149	30.20	66.0	12.0	7.3	31.0
O´Kane et al 2010	**IG**	96	42.70	57.7	**	8.8	34.0
	CG	88	36.36	60.9	**	8.6	32.0
Scherbaum et al 2008	**IG**	102	36.27	61.0	8.20	7.2	*
	CG	100	40	61.7	7.80	7.2	*
Schnell et al 2013	**IG**	226	46.46	57.0	7.70	8.9	35.1
	CG	225	47.05	54.7	7.40	8.9	35.0
Schwedes et al 2002	**IG**	113	47.78	58.7	5.46	8.47	*
	CG	110	48.18	60.5	5.22	8.35	*
Shiraiwa et al 2010	**IG**	37	*	*	*	6.7	*
	CG	34	*	*	*	6.65	*
Zhang et al 2012	**IG**	89	55.05	63.6	*	6.7	*
	CG	80	55	62.3	*	6.7	*

* no data available

** new diagnosis of T2DM

IG: Intervention Group, CG: Control group,HbA1c: Glycated Hemoglobin,BMI: Body Mass Index

Table 3. Analysis of Quality

Studies, Year	Randomisation described	Allocation concealment	Outcome assessment blinded	Withdrawals/loss to follow-up (%)	Funding
Allen et al 1990	Yes	Yes	No	11.4	Non-industry
Barnett et al 2008	Yes	Yes	Yes	14.9	Industry
Bonomo et al 2010	No	Yes	Unclear	45.7	Non-industry
Chidum et al 2011	No	No	Unclear	*	Non-industry
Dallosso et al 2014	Yes	No	No	4.45	Non-industry
Davidson et al 2005	No	Yes	Yes	18	Industry
Farmer et al 2007	Yes	Yes	Yes	12.6	Non-industry
Guerci et al 2003	No	Yes	Yes	31.0	Industry
Harashima et al 2013	No	No	Unclear	20.4	Industry
Ismail et al 2013	Yes	Yes	Unclear	5.7	Non-industry
Kempf et al 2013	No	Yes	Yes	2	Industry
Kleefstra et al 2010	Yes	Yes	Yes	2.4	Industry
Lim et al 2011	No	Yes	Unclear	6.49	Non-industry
Lu et al 2011	Yes	Yes	No	4.6	Industry
Malanda et al 2015	Yes	Yes	Yes	16.5	Industry
Nauck et al 2014	Yes	Yes	Yes	18.6	Industry
O´Kane et al 2010	Yes	Yes	Yes	2.0	Non-industry
Scherbaum et al 2008	Yes	Yes	No	16.8	Non-industry
Schnell et al 2013	No	Yes	Unclear	11.1	Industry
Schwedes et al 2002	Yes	Yes	Yes	10.8	Industry
Shiraiwa et al 2010	No	Yes	Unclear	*	Non-industry
Zhang et al 2012	No	Yes	No	*	Non-industry

* no data available

FIGURES:

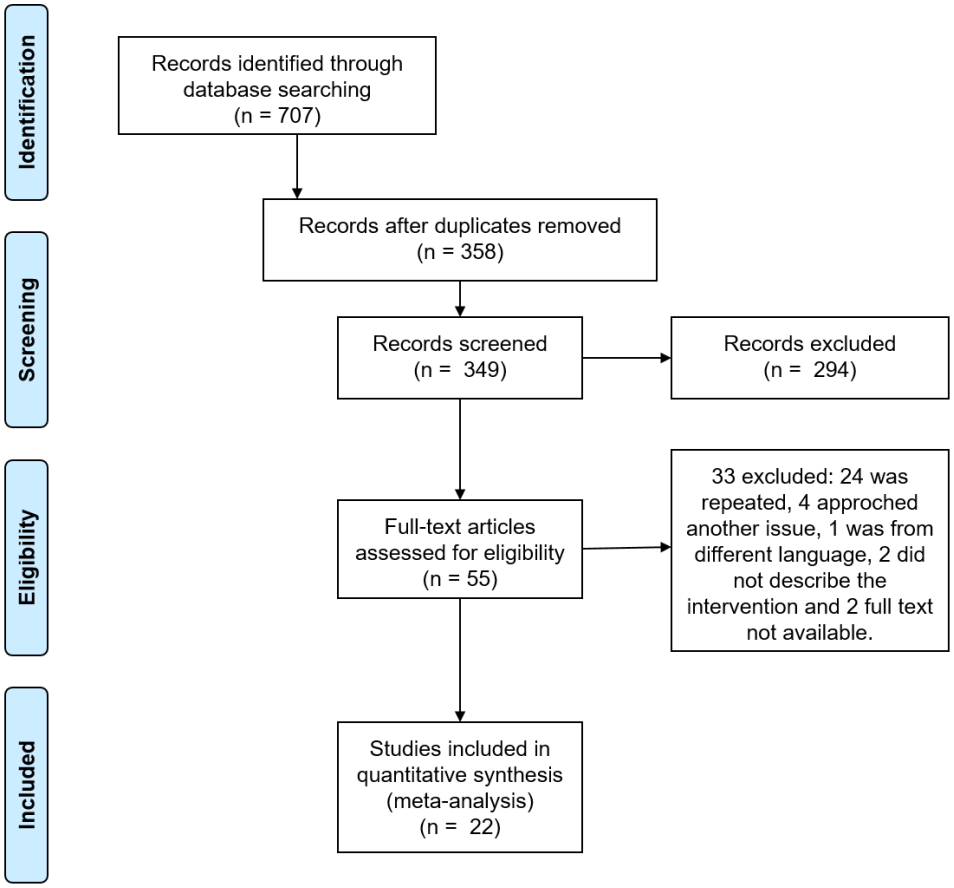

Figure 1. Flow chart to selection of studies. RCTs: Randomizes Controlled Trials; T2DM: Type 2 Diabetes Mellitus; SMBG: Self-Monitoring of Blood Glucose

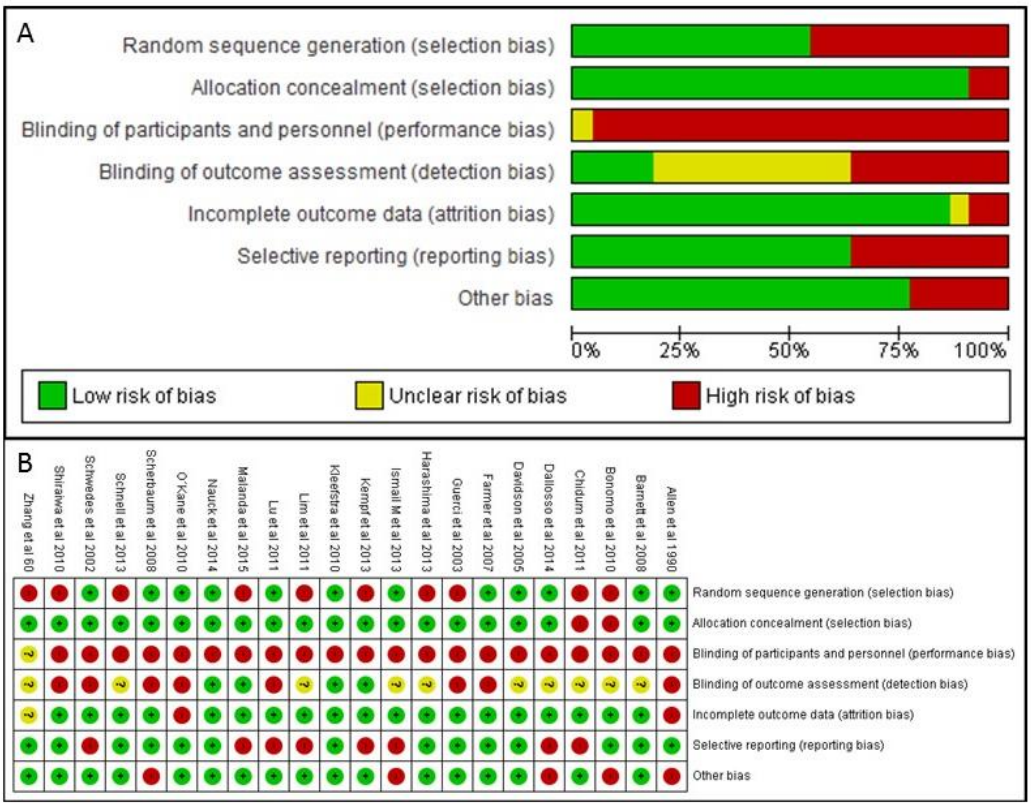

Figure 2. A. Risk of bias graph. review authors' judgements about each risk of bias item presented as percentages across all included studies. **B.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study

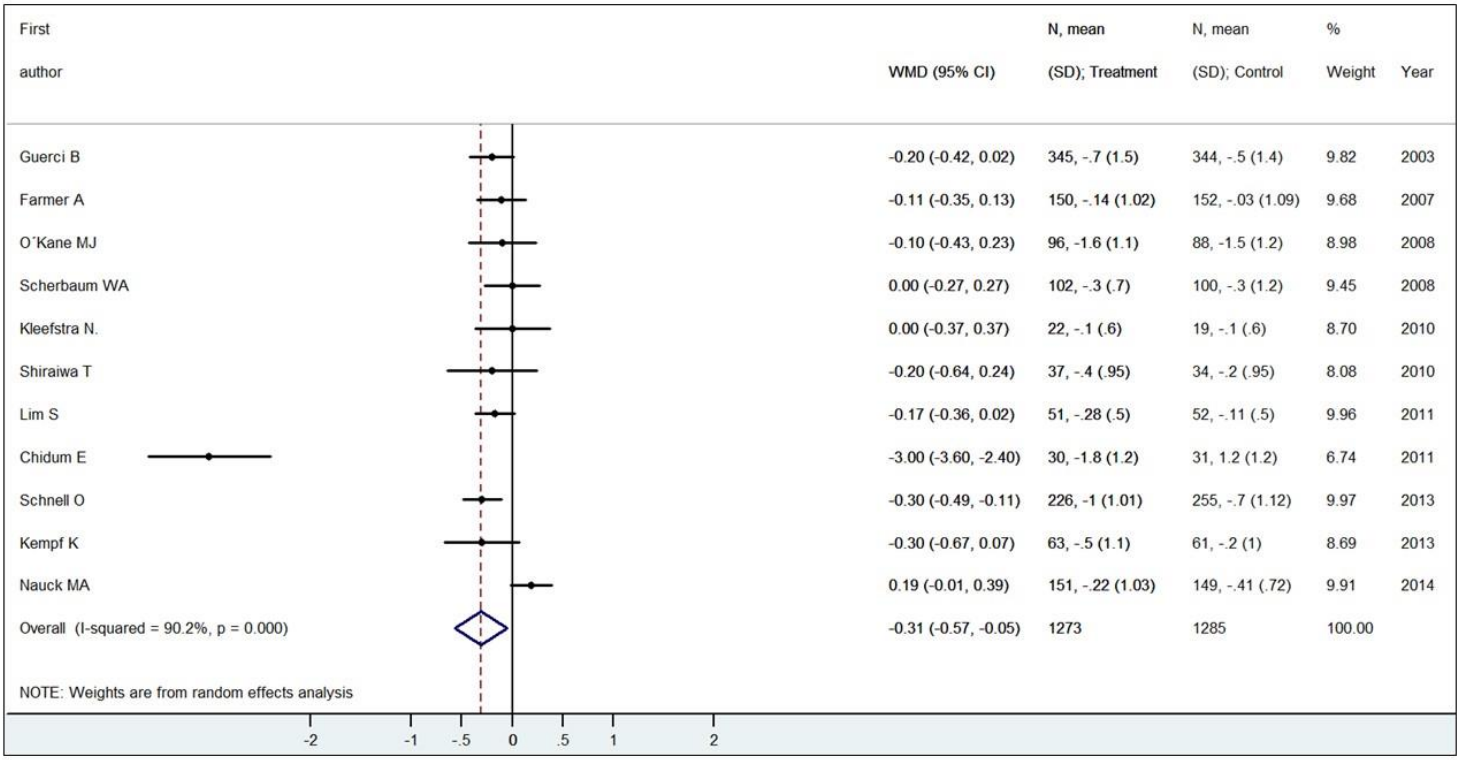

Figure 3. Forest plot of Glycated Hemoglobin (%) at 12 weeks.

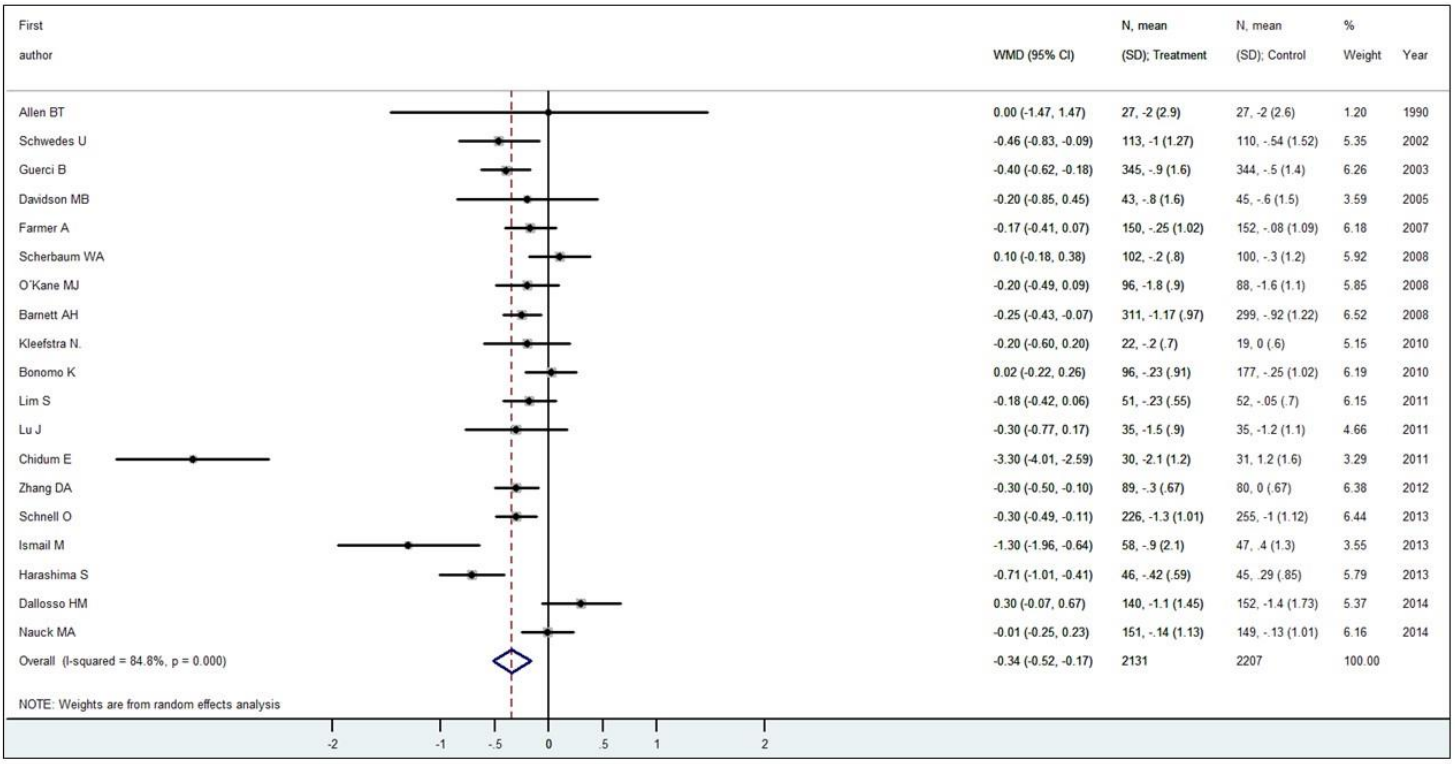

Figure 4. Forest plot of Glycated Hemoglobin (%) at 24 weeks.

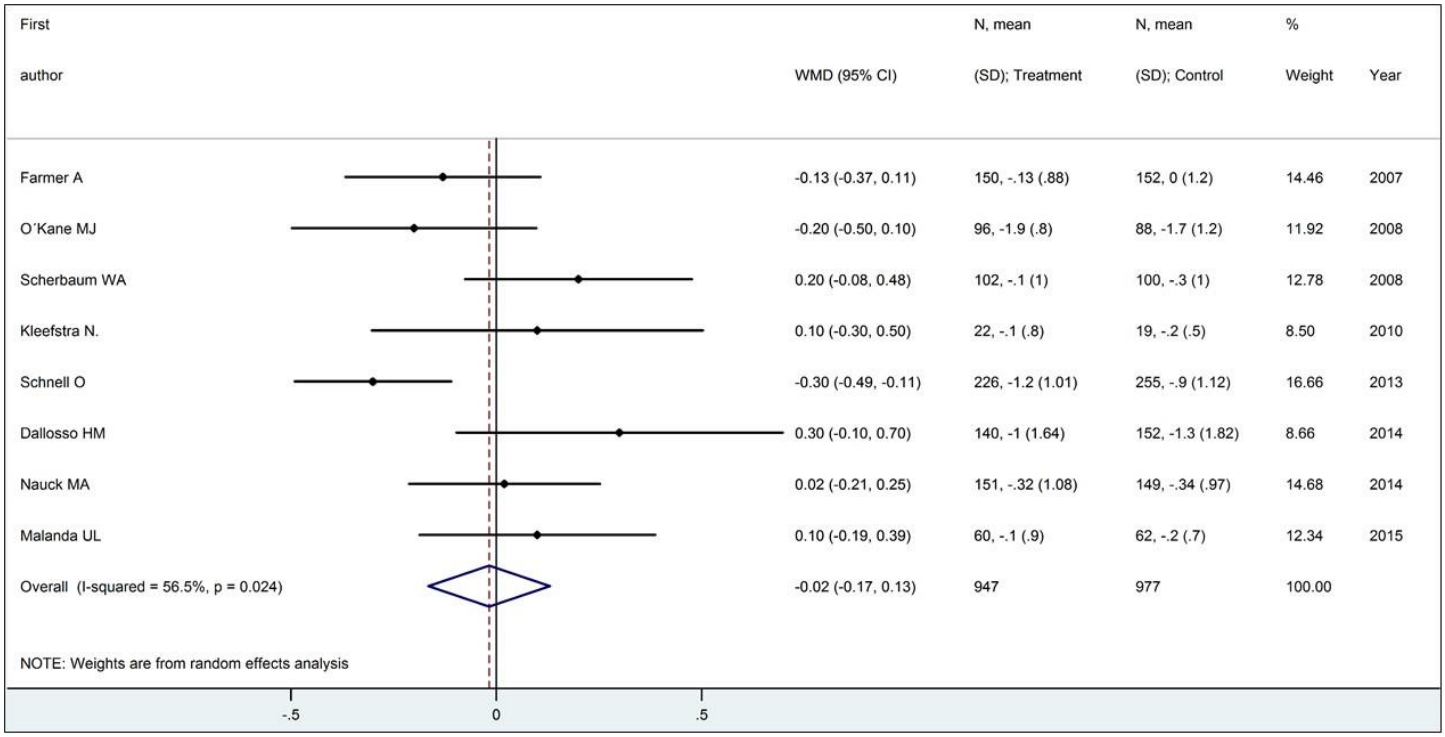

Figure 5. Forest plot of Glycated Hemoglobin (%) at one-year.

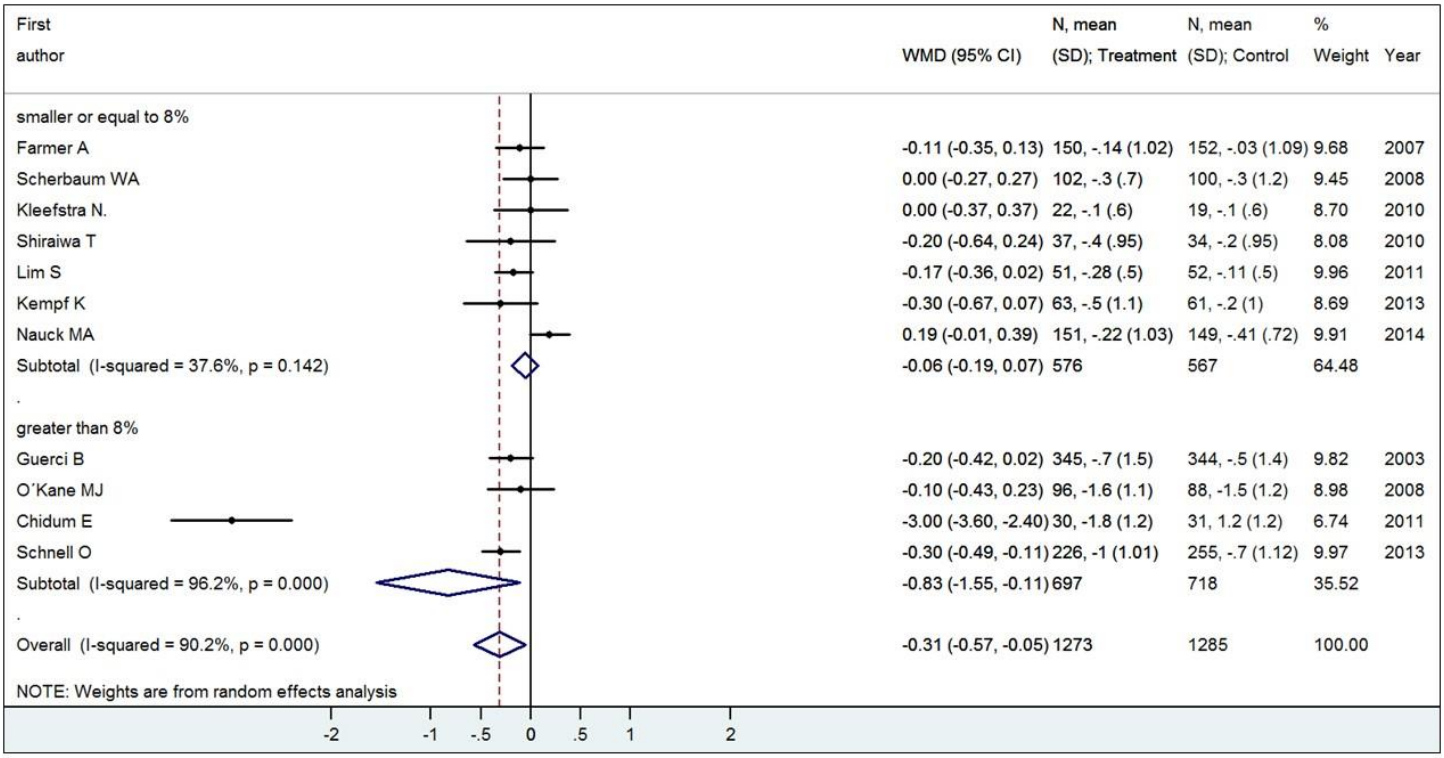

Figure 6. Forest plot of Glycated Hemoglobin (%) at 12 weeks. Subgroup analysis of greater than 8% or smaller or equal 8%.

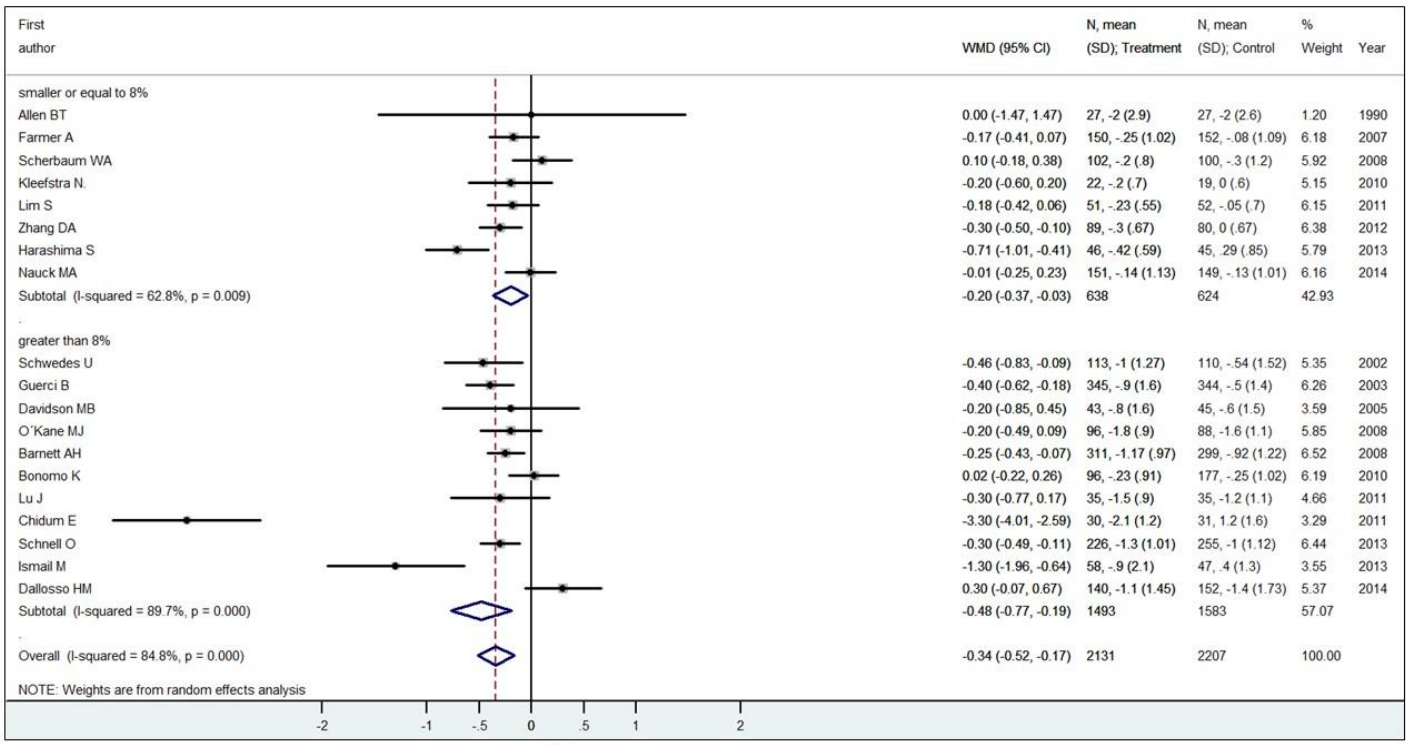

Figure 7. Forest plot of Glycated Hemoglobin (%) at 24 weeks. Subgroup analysis of greater than 8% or smaller or equal 8%.

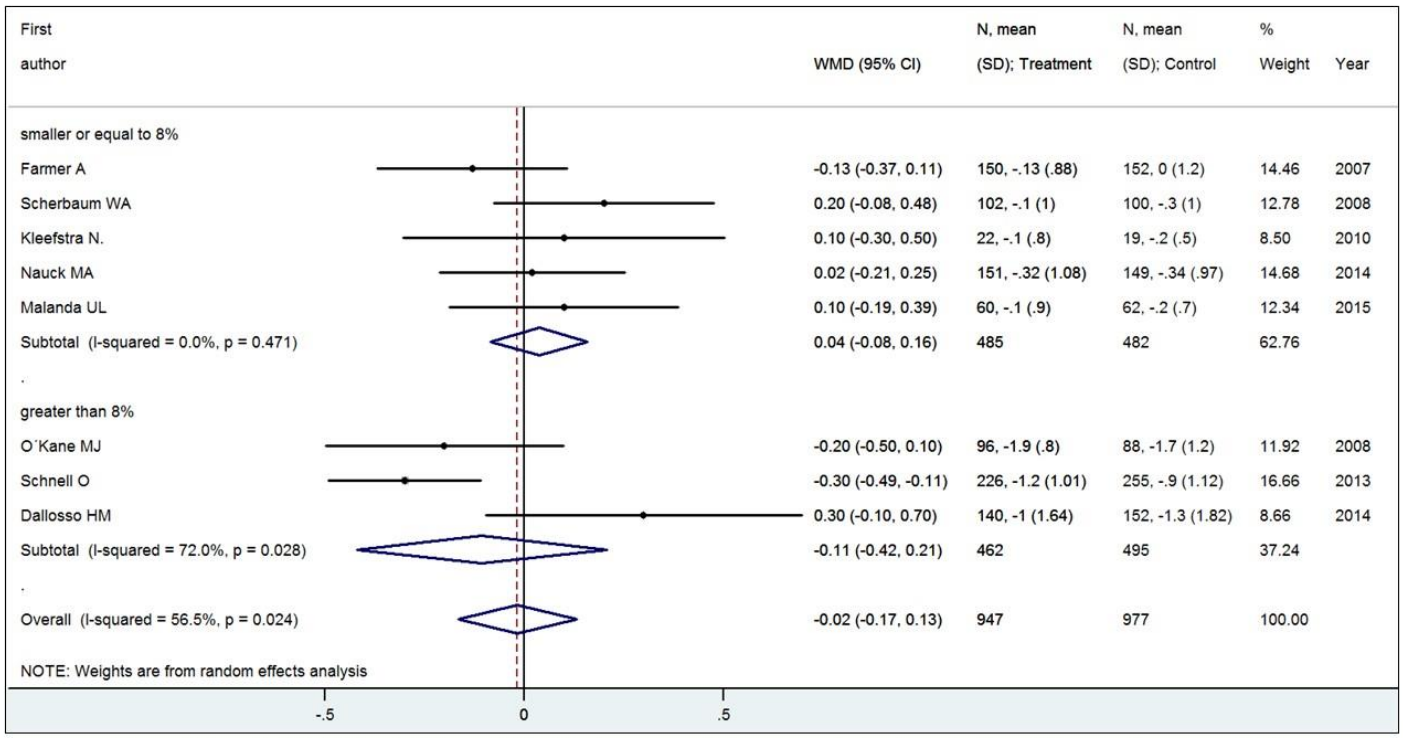

Figure 8. Forest plot of Glycated Hemoglobin (%) at one-year. Subgroup analysis of greater than 8% or smaller or equal 8%.

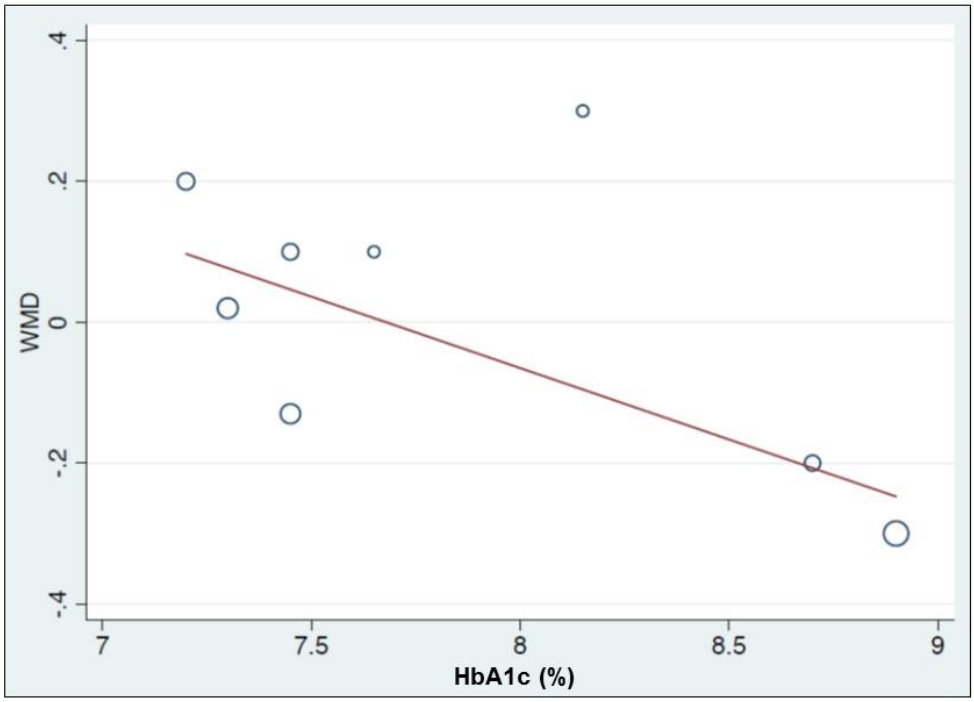

Figure 9. Bubble Plot to Meta Regression to baseline values of Glycated Hemoglobin (HbA1c) at one-year of follow-up. Solid line represent linear predictions of de WMD between intervention (SMBG) and control group. The bubbles are the mean difference in each study with bubble sizes proportional to the study weight. WMD: Weighted Mean Difference.

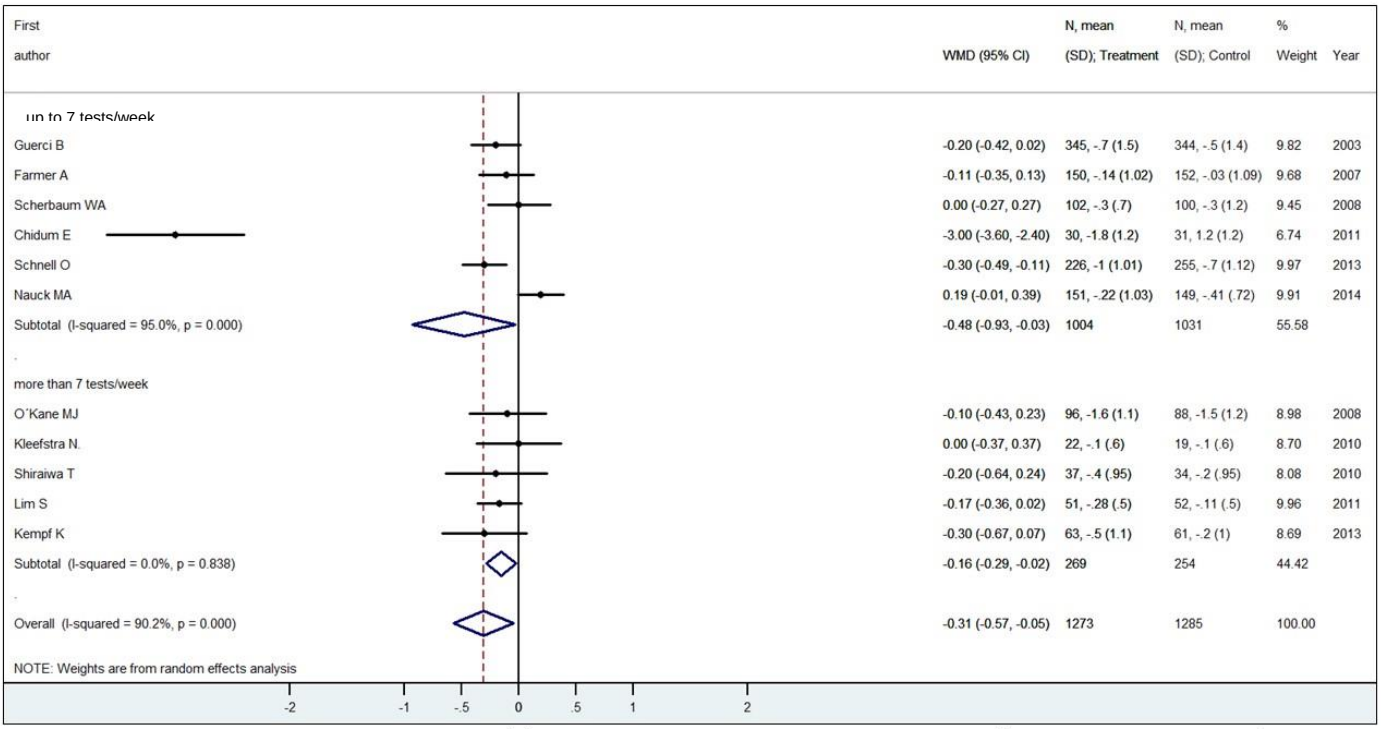

Figure 10. Forest plot of Glycated Hemoglobin (%) at 12 weeks. Subgroup analysis of at least 7 tests/week or more than 7 tests/week.

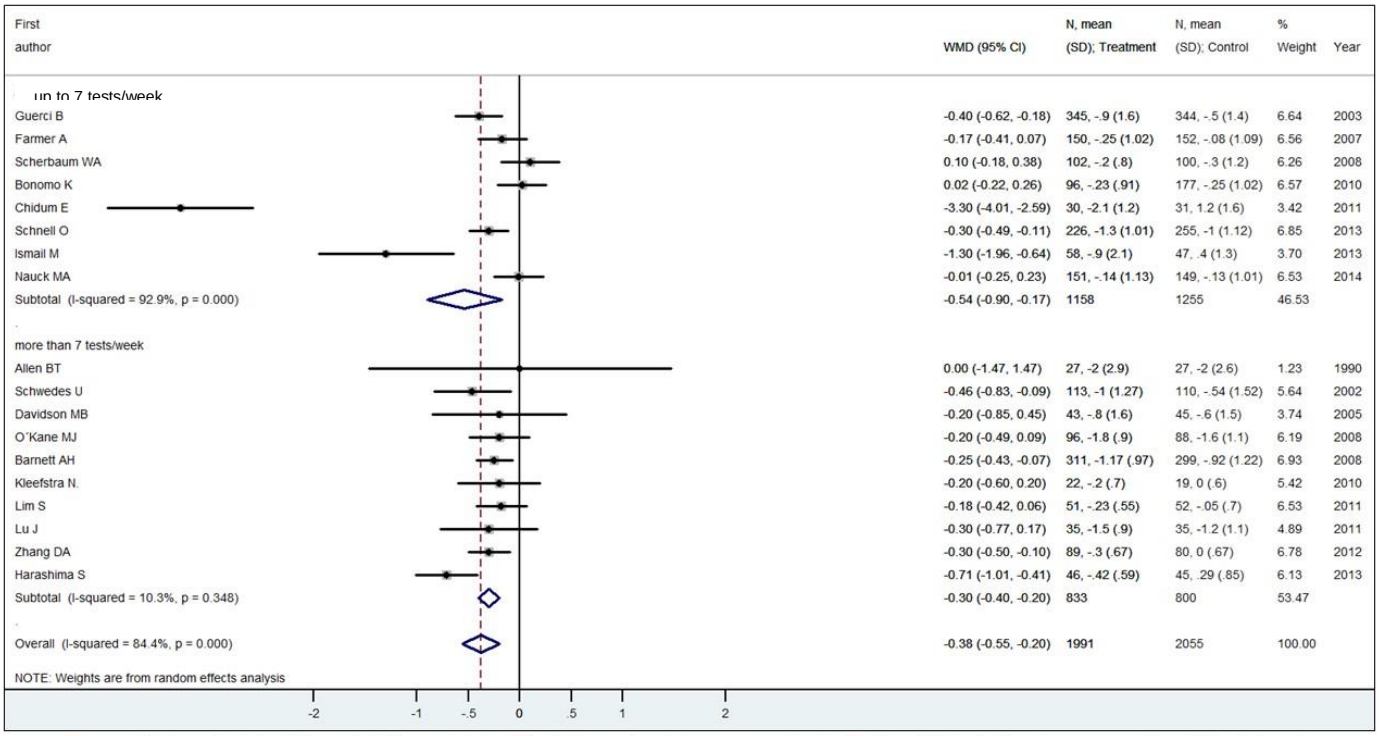

Figure 11. Forest plot of Glycated Hemoglobin (%) at 24 weeks. Subgroup analysis of at least 7 tests/week or more than 7 tests/week.

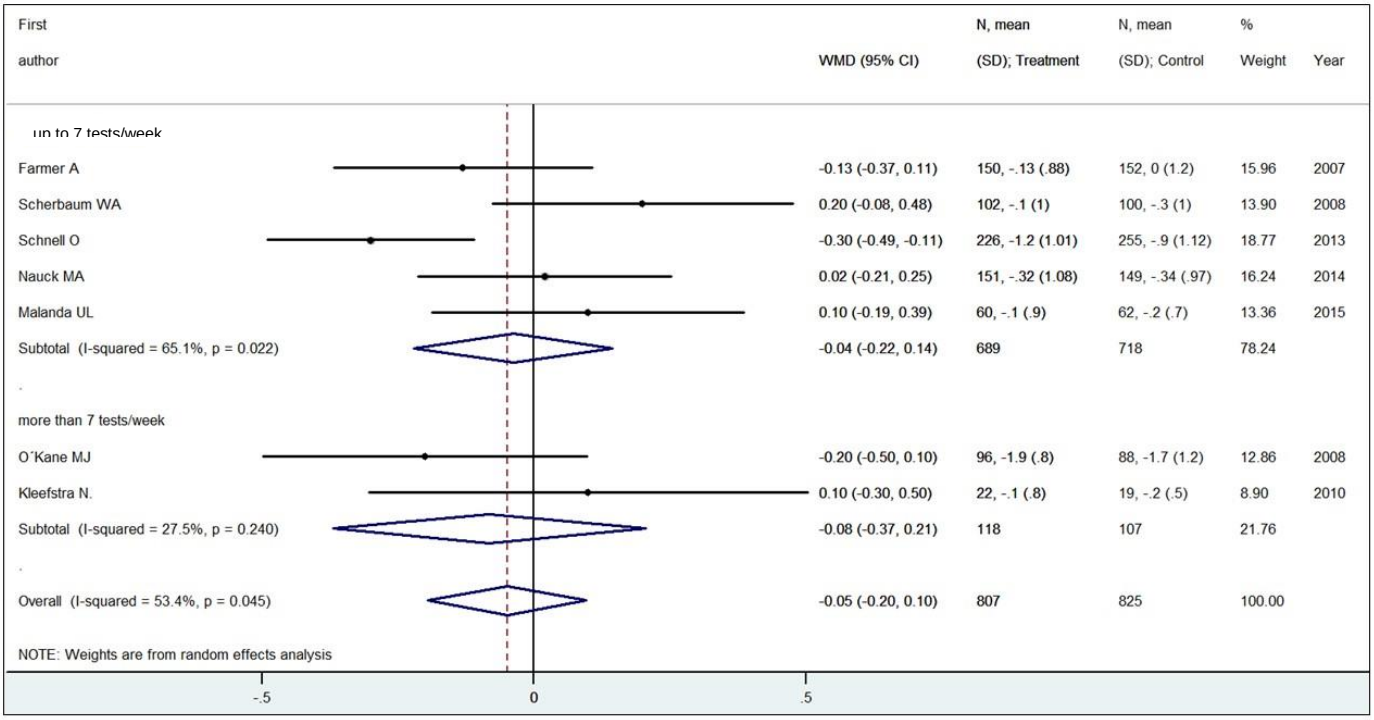

Figure 12. Forest plot of Glycated Hemoglobin (%) at one year. Subgroup analysis of at least 7 tests/week or more than 7 tests/week.

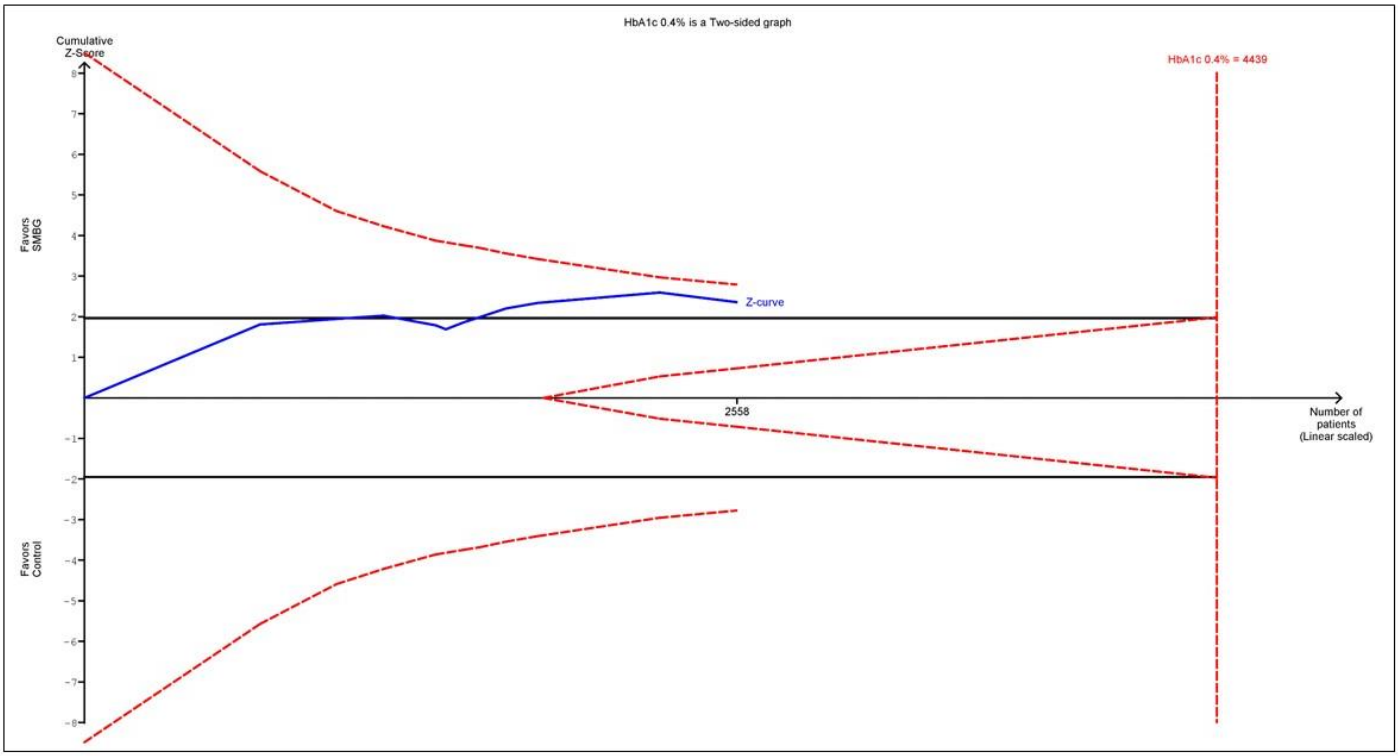

Figure 13. TSA for Glycated Hemoglobin at 12 weeks. Difference of 0.4% in HbA1c between the groups (SMBG and comparator) with α of 5%, a β of 80% . The blue line is the Z curve (cumulative effect), the red dashed lines is the harm, benefit, and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis, and the black lines is the conventional confidence intervals. The black number and marking in the x-axis is the number of patients accrued until each point.

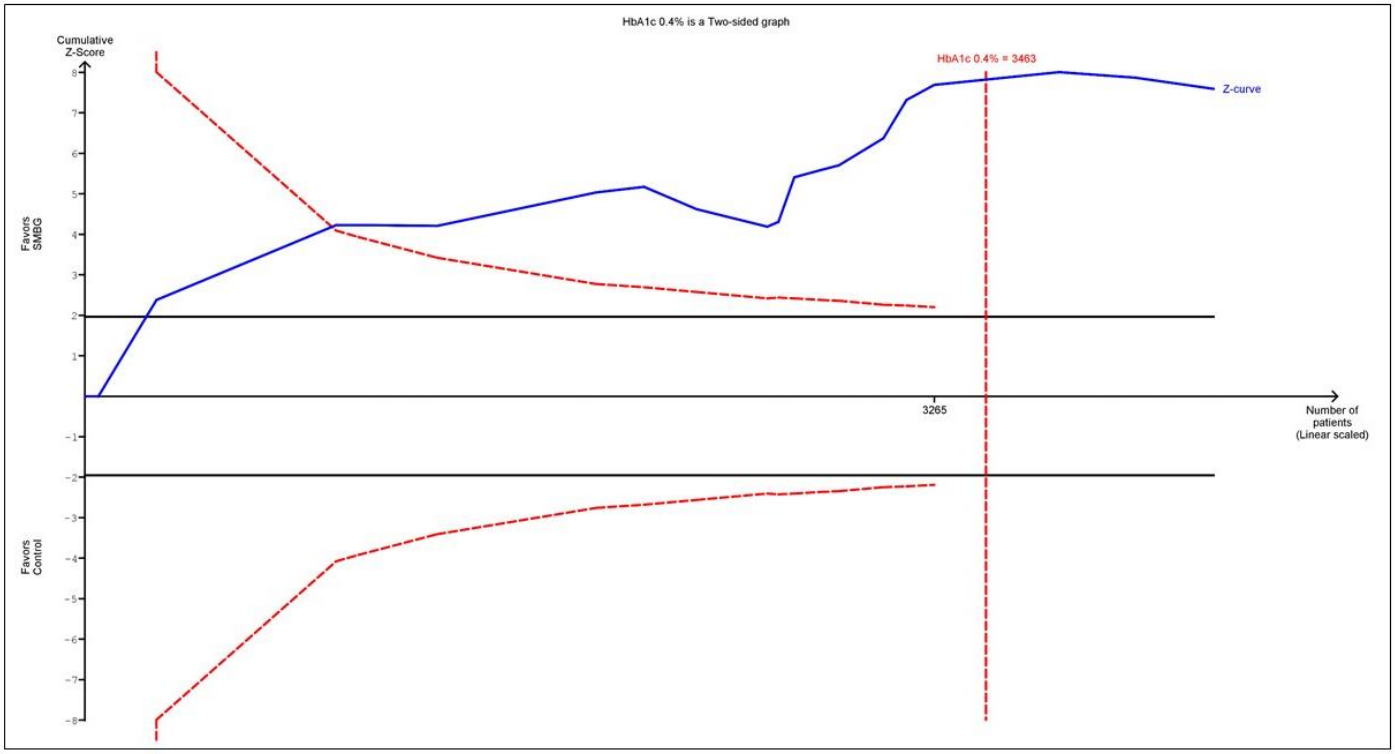

Figure 14. TSA for Glycated Hemoglobin at 24 weeks. Difference of 0.4% in HbA1c between the groups (SMBG and comparator) with α of 5%, a β of 80% . The blue line is the Z curve (cumulative effect), the red dashed lines is the harm, benefit, and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis, and the black lines is the conventional confidence intervals. The black number and marking in the x-axis is the number of patients accrued until each point.

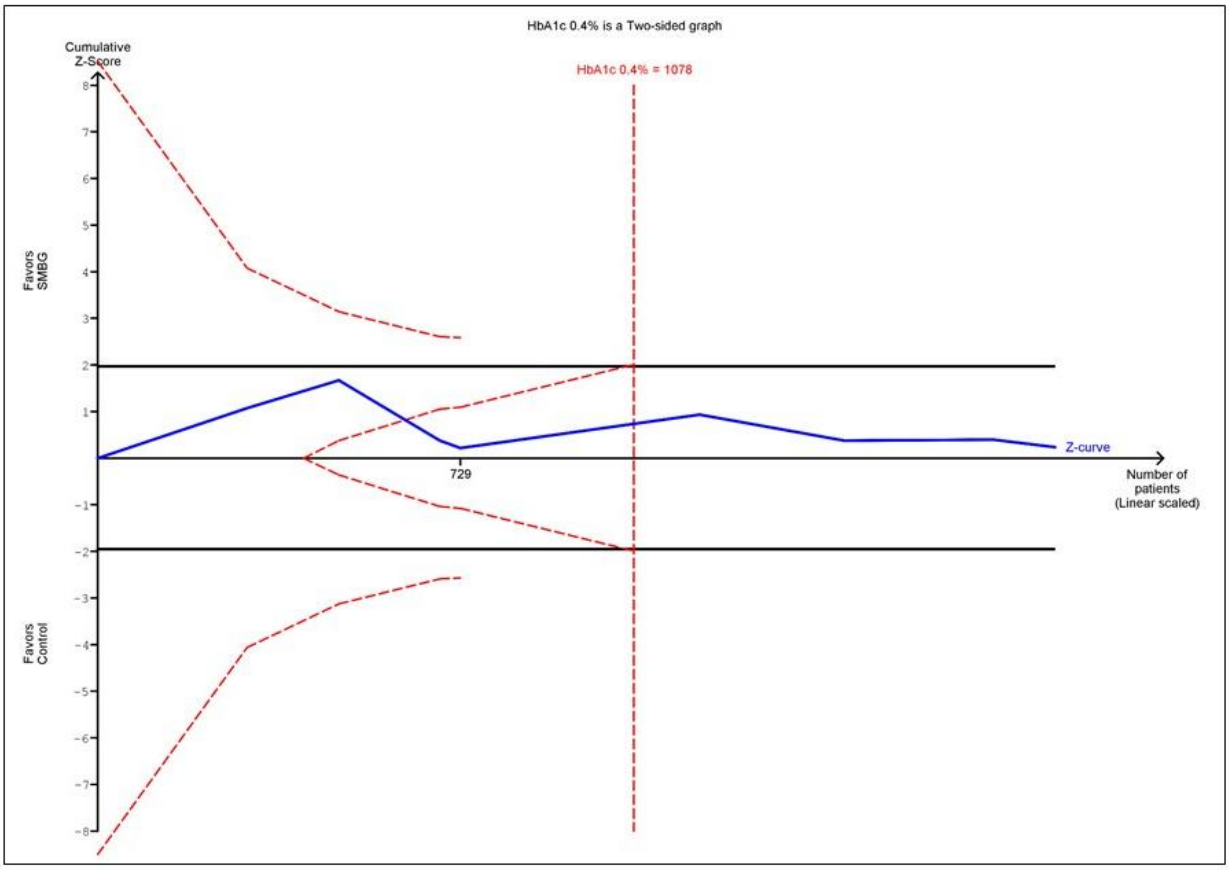

Figure 15. TSA for Glycated Hemoglobin at one year. Difference of 0.4% in HbA1c between the groups (SMBG and comparator) with α of 5%, a β of 80% . The blue line is the Z curve (cumulative effect), the red dashed lines is the harm, benefit, and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis, and the black lines is the conventional confidence intervals. The black number and marking in the x-axis is the number of patients accrued until each point.

CONCLUSÕES

O Diabetes é uma doença crônica, com progressão para múltiplas complicações. Ao longo dos anos de vida, a prevalência é crescente, e vai de encontro às dificuldades para manejo e aderência às terapias necessárias.

Mais do que novos medicamentos, estratégias não farmacológicas podem auxiliar no manejo dos pacientes com DM2 que estão com dificuldades de alcançar valores adequados de HbA1c. Além disso, estas medidas podem ser inseridas no grupo de insumos disponíveis pelo Sistema Único de Saúde. O uso de canetas para aplicação de insulina, tanto como integrante de medidas multifatoriais quanto isoladamente, auxilia na melhora do controle glicêmico. A redução de HbA1c, em 24 semanas do uso deste método, se apresentou em valores clinicamente significativos nos dois primeiros estudos desta Tese de Doutorado. Além disso, estes resultados puderam ser alcançados com auxílio de outras medidas no manejo dos pacientes. O acompanhamento estreito com o médico, para ajustes frequentes do tratamento, parece estar inserido entre as medidas importantes para os cronicamente descompensados. E neste sentido, uma grande reformulação no atendimento dos pacientes do SUS precisa ser realizada, não é possível um manejo adequado desta doença realizado à distância com poucas visitas ao médico ao ano.

A AMGC esteve incluída nas medidas realizadas nos dois primeiros estudos. Para a avaliação individualizada sobre o controle glicêmico, os resultados do terceiro estudo identificam que a aferição da glicemia capilar pode auxiliar na redução dos valores de HbA1c nas primeiras 24 semanas, principalmente entre pacientes sem controle glicêmico adequado. Porém, estes valores não são tão imponetes frente ao uso das canetas de insulina. O efeito do método parece se perder ao longo de um ano.

De modo que é preciso entender o benefício da AMGC no contexto do SUS e indicá-lo de modo correto.

PERSPECTIVAS

O desenvolvimento desta Tese de Doutorado e vínculo na Pós Graduação foi essencial para firmar meu compromisso com a ciência e confirmar o gosto pela pesquisa. Os estudos desenvolvidos ao longo deste período servem de pedra fundamental para seguir a carreira acadêmica. Recentemente, fui aprovado em Concurso Público para Docente do Curso de Medicina da Universidade Federal de Santa Maria-RS, em breve devo assumir cargo como Professor Adjunto, onde já estou desenvolvendo outros projetos paralelos. Pretendo seguir na linha de pesquisa de Educação em Diabetes, em busca de respostas às perguntas que enfrentamos no dia-a-dia da prática médica.

Nos próximos meses, pretendo concluir a coleta de dados do Estudo 2, apresentado nesta tese com dados parciais, para corroborar os resultados já encontrados.

Há também a perspectiva do desenvolvimento de um Ensaio Clínico Randomizado para testar a influência da realização de testes de glicemia capilar entre pacientes com DM2 em uso de insulina, sem tratamento intensivo (dado não apresentado na literatura atual), este projeto foi apresentado em meu Exame de Qualificação Geral de Doutorado. Neste mesmo estudo, poderemos definir o número correto de testes de glicemia capilar que devem ser recomendados para esta população de pacientes com DM 2 usuários de insulina e fora de esquema intensivo.

Além dos estudos apresentados aqui, também estou desenvolvendo, como pesquisador colaborador, outros três estudos na área de Endocrinologia. O primeiro refere-se ao uso de topiramato para redução de peso em pacientes com Síndrome dos Ovários Policísticos, o segundo em relação a valores preditores de vitamina D, paratormônio, e cálcio para hipoparatireoidismo pós tireoidectomia. O último refere-se

à avaliação do desenvolvimento de disfunção tireoidiana em crianças expostas à organofosforados da indústria fumageira do interior do Rio Grande do Sul.

Em conclusão, pretendo seguir na carreira acadêmica, tanto no anseio de formar médicos completos e melhor preparados para os desafios da profissão, quanto para produzir informação científica de qualidade. Além do crescimento pessoal, contribuir para a projeção nacional e internacional da Universidade na qual me formei, fazem parte dos meus sonhos para a minha carreira futura.

Minha tese de doutorado possui outra extensão que será parte da tese de doutorado de colega farmacêutica que esta trabalhando em dados de custo-efetividade de nossa intervenção em relação à redução de HbA1c. A definição do ônus aos cofres públicos em comparação aos custos diretos e indiretos que o Diabetes traz aos brasileiros (internações hospitalares, visitas às emergências, uso de mais medicamentos, por exemplo) é assunto de grande relevância.