UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Avaliação da Eficácia de Ligações Telefônicas para o Controle Glicêmico no Diabetes Mellitus tipo 2: Revisão Sistemática com Metanálise e Ensaio Clínico Randomizado

Tese de Doutorado

Ana Marina da Silva Moreira

Porto Alegre, 2020

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Dedicatória

"À minha mãe Cleide Moreira que me ensinou
que eu poderia ser o que eu quisesse"

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Lista de Siglas e Abreviações

DM – *Diabetes Mellitus*

DM2 – *Diabetes Mellitus tipo 2*

T1DM – *Type 1 Diabetes Mellitus*

GRADE – *Grading of Recommendations, Assessment, Development and Evaluations*

PROSPERO – *International Prospective Register of Systematic Reviews*

PRISMA - *Preferred Reporting Items for Systematic Reviews and Meta-analysis*

CONSORT- *Consolidated Standards of Reporting Trials*

RCT –*randomized controlled trial*

RR – *relative risk*

SD – *standard deviation*

SBP – *systolic blood pressure*

DBP *- diastolic blood pressure*

SMBG - *Self-monitoring Blood Glucose*

TSA – *Trial sequential analysis*

RESUMO

O DM2 é um problema de saúde pública com crescente prevalência na população mundial. Em virtude do custo associado à doença e da necessidade de melhor controle glicêmico para prevenção das complicações crônicas, a criação de novas ferramentas para auxílio ao atendimento do paciente diabético se faz necessária. Nesse contexto, a telemedicina vem sendo uma alternativa bastante atual e promissora, com crescente número de estudos disponíveis na literatura na última década.

Entre as diversas ferramentas disponíveis de telemedicina, optamos por estudar mais especificamente as ligações telefônicas, devido à sua ampla utilização no cotidiano dos pacientes, sendo aplicável à realidade e aos recursos do sistema de saúde público brasileiro. Apresentamos nossa evidência por meio de dois delineamentos de alta qualidade: o ensaio clínico randomizado (ECR) e a revisão sistemática com metanálise de ECRs, o que nos permite maior grau de certeza nas nossas conclusões.

Avaliando primeiramente a eficácia desta intervenção no controle glicêmico de pacientes com DM2, realizamos uma revisão sistemática com metanálise de 28 ECRs (7952 pacientes), com o objetivo central de sintetizar a informação disponível até o momento. Em todos os estudos incluídos, o principal conteúdo abordado nas ligações telefônicas era a educação em DM2 e o estímulo ao autocuidado. Verificamos uma redução estatisticamente significativa em HbA1c (-0,34%) nos pacientes que foram submetidos a ligações telefônicas periódicas quando comparados aos cuidados de rotina, sendo este benefício mais expressivo quando a intervenção era realizada por enfermeiras (redução de 0.54% em HbA1c). No entanto, a elevada heterogeneidade encontrada pelo nosso estudo ($I^2$80%) limita a consistência e a qualidade da nossa evidência. Na tentativa de explorar a heterogeneidade, conduzimos análises de subgrupo e meta-regressão para diversos fatores com possível influência no resultado encontrado, porém não houve nenhuma associação evidente, nos permitindo concluir que a inconsistência dos nossos achados se deve aos próprios estudos (intervenção com abordagens

variadas, populações de diferente nível cultural, grupos controle com diferentes contextos de saúde, tamanho amostral variável). Além disso, a diferença numérica encontrada na HbA1c (-0,34%) não apresenta relevância clínica por estar dentro do coeficiente de variabilidade biológica do próprio método laboratorial. Portanto, apesar da melhora numérica da HbA1c e da tendência a benefício das ligações telefônicas no manejo do DM2, a eficácia clínica desta abordagem ainda não está demonstrada e os estudos disponíveis até o momento são muito heterogêneos. São necessários, portanto, ECRs mais bem delineados e com uma descrição mais detalhada dos grupos em estudo e da intervenção proposta para que seja possível inferir a existência de benefício das ligações telefônicas no controle glicêmico do paciente diabético.

Para um melhor estudo desta intervenção, realizamos também um ensaio clínico randomizado com 147 pacientes DM2 com controle glicêmico razoável, sem complicações crônicas graves e com critérios de alta de um serviço terciário para a atenção primária. Além da avaliação da eficácia das ligações telefônicas no controle glicêmico, foi possível avaliar o papel de uma intervenção em telemedicina na contrarreferência desses pacientes, um estudo pioneiro na literatura até então. Os pacientes incluídos foram randomizados em grupo intervenção (atenção primária + ligações telefônicas trimestrais; n = 73) e controle (atenção primária; n = 74) e avaliados após 1 ano da alta de serviço especializado. As ligações telefônicas eram realizadas por enfermeiras treinadas e tinham ênfase em educação em DM2. Se observou uma piora numérica estatisticamente significativa da HbA1c em ambos os grupos após 1 ano de seguimento [7,0± 0,67% no basal para 7,46± 1,37% aos 12 meses no grupo intervenção ($p<0,001$) versus 6,9± 0,7% no basal para 7,54±1,6% aos 12 meses no grupo controle ($p=0,002$)]. Conforme o coeficiente de variabilidade biológica e laboratorial do método da HbA1c, a piora no grupo intervenção não foi clinicamente significativa. Além disso, a proporção de pacientes que atingiram o alvo glicêmico almejado se manteve após os 12 meses, nos permitindo concluir que a alta ambulatorial de um serviço terciário em pacientes com DM2 bem controlado e sem complicações crônicas graves é segura e não está relacionada a descompensação do DM2. Este

achado pode servir como estímulo à alta de ambulatórios especializados, colaborando para uma redução da superlotação do serviço terciário e um melhor fluxo da rede integrada de saúde.

Em conclusão, as informações apresentadas nesta tese são úteis para a prática clínica e apresentam uma grande relevância em termos de saúde pública. As ligações telefônicas têm tendência a contribuir para a melhora no controle glicêmico dos pacientes com DM2, mas ainda sem benefício clínico estabelecido e com necessidade de estudos mais bem delineados. Avaliando a contrarreferência para a atenção primária, concluímos ainda, que em pacientes com DM2 bem compensado e com critérios de alta ambulatorial de serviço terciário, as ligações telefônicas não estão associadas a melhora do controle glicêmico. No entanto, a alta ambulatorial e a contrarreferência para a atenção primária são seguras e os pacientes se mantêm no alvo glicêmico estabelecido. Assim, o conhecimento gerado por esta tese aprofunda um tema bastante atual e com potencial utilidade na prática clínica e apresenta um campo de pesquisa ainda a ser explorado.

INTRODUÇÃO

O diabetes mellitus (DM) é considerado um problema de saúde pública mundial. De acordo com a *International Diabetes Federation* (IDF), o DM se apresenta como uma das doenças de crescimento mais rápido do século XXI. Em 2019, a prevalência mundial estimada chegou a 463 milhões de adultos com DM, com uma expectativa de aumento para 700 milhões de pacientes acometidos pela doença em 2045 [1]. Analisando o contexto mundial, os países subdesenvolvidos e em desenvolvimento apresentam a maior parte destes casos, concentrando cerca de 80% dos pacientes com DM. Além disso, os países com menores índices de desenvolvimento também apresentam as maiores de taxas de pacientes diabéticos não diagnosticados, 66% dos casos, fato decorrente provavelmente do limitado acesso à saúde [1,2].

O Brasil atualmente ocupa a quinta posição entre os países com maior prevalência de DM no mundo, chegando em 2019 a 16,8 milhões de diabéticos, com expectativa de aumento relativo de 55% até 2045, totalizando aproximadamente 26 milhões de pacientes com a doença no país [1]. O diabetes mellitus tipo 2 (DM2) corresponde a cerca de 90% dos casos de DM no mundo e apesar de multifatorial, o seu avanço nas últimas décadas pode ser explicado pelo aumento dos índices de obesidade, favorecendo a resistência insulínica implicada na patogênese da doença e consequentemente, a hiperglicemia [3].

Complicações crônicas do DM

A hiperglicemia crônica está associada ao desenvolvimento das complicações do DM, acarretando um aumento da morbidade e mortalidade relacionadas à doença. Estima-se que

cerca de 50% dos pacientes com DM2 apresentem complicações microvasculares, sendo que 25% já as manifestam ao diagnóstico [4,5]. A doença renal do diabetes afeta de 25-50% dos pacientes e é a principal causa de doença renal terminal, contabilizando cerca de 50% dos casos no mundo [5,6]. Já a retinopatia diabética representa a principal causa estabelecida de cegueira, geralmente atribuída ao edema macular e à sua forma proliferativa, estágio avançado do dano à microvasculatura da retina. A neuropatia diabética é a complicação mais comum do DM, surgindo em 50% dos pacientes após 10 anos de evolução. Entre os seus subtipos, a neuropatia cardiovascular autonômica é apontada como um fator de risco independente para isquemia silenciosa e mortalidade cardiovascular [5].

As complicações macrovasculares ocorrem em 27% dos pacientes com DM, aumentando substancialmente seu risco cardíaco e mortalidade [4]. Em revisão sistemática publicada em 2015, Vaidya et al. estimou uma variação de prevalência de complicações cardiovasculares no DM2 de 22-64%, sendo a hipertensão, a complicação mais comum. Ainda nesta revisão sistemática, foi demonstrada uma taxa de mortalidade cardiovascular de cerca de 40% nessa população [7]. Os possíveis fatores de risco relacionados à mortalidade cardiovascular no DM2 são idade mais jovem, mau controle glicêmico e complicações renais graves associadas [8]. Apesar da ainda elevada prevalência, dados de países desenvolvidos apontam uma redução da ocorrência das doenças macrovasculares do diabetes e da mortalidade por todas as causas nas últimas duas décadas. Isto leva a um aumento da expectativa de vida desta população, gerando um maior tempo de exposição à hiperglicemia e aumentando a morbidade e os custos associados ao tratamento das demais complicações crônicas [9,10].

O diabetes apresenta custos diretos e indiretos, representando um problema mais expressivo principalmente para países de economia incipiente. A IDF estimou uma média mundial de gastos de 760 bilhões de dólares em custos diretos com a doença em 2019. O Brasil,

atualmente, ocupa a terceira posição entre as economias com maiores gastos diretos associados ao DM, cerca de 52,3 bilhões de dólares investidos em 2019. Como custos indiretos, são considerados: perda de força de trabalho, mortalidade e absenteísmo [1]. Considerando que o DM acomete principalmente indivíduos em idade produtiva, a doença tem um impacto muito negativo para a economia mundial. Desta forma, medidas que otimizem os recursos públicos são estratégias fundamentais para o planejamento do controle do diabetes.

Atenção primária à saúde e Telemedicina

Por se tratar de uma doença de alta prevalência, grande parte dos pacientes com DM são atendidos em atenção primária à saúde (APS) e, portanto, a qualificação deste nível de cuidado é essencial para um melhor atendimento e uma adequada alocação de recursos. De acordo com o *Global Diabetes Plan (2011-21)*, a *World Health Organization* (WHO) enfatiza a importância da construção e do fortalecimento da APS para melhorar a acessibilidade do paciente e os desfechos associados à doença [11]. Além disso, o DM2 é considerado uma condição sensível à APS.

A equipe de saúde da família (ESF) deve ser capaz de realizar desde o diagnóstico até o manejo das possíveis complicações crônicas do paciente com DM [11]. No entanto, a APS enfrenta alguns problemas que limitam a qualidade do cuidado. Mundaliar et al. em 2013, através de uma revisão sistemática realizada em países da América Central e do Sul, constatou que a frequência observada de pacientes fora do alvo glicêmico variou de 49-92% entre os estudos, resultado muito aquém do recomendado pela literatura. Apontaram-se ainda como principais barreiras enfrentadas na atenção primária: ausência de motivação e baixo nível educacional do paciente, ausência de tempo do médico para esclarecer regimes terapêuticos complexos e limitado acesso ao cuidado (financeiro e geográfico) [12].

As dificuldades enfrentadas pela atenção primária geram encaminhamentos desnecessários e superlotação dos serviços terciários, com redução do acesso do paciente à rede de saúde no nível adequado. Uma rede de saúde integrada com abordagem de natureza preventiva e multidisciplinar é fundamental para o manejo e redução das complicações de doenças crônicas como o diabetes [13].

Atualmente, o Sistema Único de Saúde (SUS) enfrenta desafios associados à fragmentação existente entre os serviços de atenção primária e terciária. Os serviços especializados com alta qualidade e tecnologia estão disponíveis, mas não são capazes de absorver a crescente demanda [14]. Desta forma, o desenvolvimento de ferramentas que possam auxiliar a equipe da atenção primária no cuidado ao paciente diabético e a otimizar seu atendimento é de fundamental importância para a integralização da rede de cuidado e consequentemente para a melhora do acesso do paciente ao sistema de saúde.

Neste contexto, a telemedicina desponta como uma alternativa promissora para auxiliar o treinamento das equipes de saúde da família e o melhor direcionamento dos encaminhamentos para serviços especializados com redução nas filas de espera [15]. De acordo com o Instituto de Medicina, telemedicina é definida como o uso de informações eletrônicas e tecnologias de comunicação para promover e apoiar o sistema de saúde quando a distância separa os participantes envolvidos [16]. O termo telemedicina geralmente é empregado em um contexto de assistência em saúde. Já a expressão telessaúde, é utilizada em um contexto mais amplo, englobando, além disso, a educação em saúde e a telemonitorização, definida como a utilização de tecnologias à distância para o seguimento do paciente em suas atividades diárias [17].

De acordo com a *American Diabetes Association (ADA)*, existem crescentes evidências no uso da telemedicina no diabetes, com uma tendência à melhora do controle glicêmico [18]. Em uma scoping review publicada em 2019, Borries et al. apontaram um efeito positivo na

hemoglobina glicada (HbA1c) relatado em 71% dos estudos que avaliaram o uso da telemedicina no DM, mas com pouca evidência disponível avaliando desfechos em longo prazo [19]. Em 2013, Marcolino et al. apontaram uma melhora de 0,44% na HbA1c (IC 95% -0,61, -0,26%) a favor da telemedicina em metanálise de 13 ensaios clínicos randomizados (ECR), porém com elevada heterogeneidade ($I^2$73%) [20]. Quanto à eficácia da telemedicina no contexto da atenção primária, So et al. publicaram em 2017 uma metanálise de 7 ECRs que apresentou uma redução em HbA1c de 0,64% (IC 95% -1,01, -0,26; $I^2$89%) [21]. Também em 2017, Heitkemper et al. estudaram através de revisão sistemática de 10 ECRs, os efeitos de diversas abordagens em telemedicina (mensagens de texto, softwares, aplicativos de internet, videoconferências) em pacientes com DM2 atendidos em atenção primária pertencentes a minorias ou habitantes de áreas pouco desenvolvidas. Verificou-se uma redução em HbA1c após 6 meses de intervenção de 0,36% (IC 95% -0,13, -0,19; $I^2$35%), favorecendo as intervenções em telemedicina [22]. Corroborando os resultados anteriores, em 2018, Lee et al. demonstraram também através de metanálise, um benefício em HbA1c de 0,55% (IC 95%: -0,73, -0,36) a favor da telemedicina, com uma redução mais expressiva quando a intervenção era através de ligações telefônicas (queda de 0,88%), porém com elevada heterogeneidade ($I^2$86%) [23]. Isto sugere uma inconsistência ainda não explorada entre os estudos existentes e uma necessidade de uma avaliação mais detalhada da eficácia desta intervenção no DM.

As ligações telefônicas constituem uma aplicação da telemedicina com baixo custo e complexidade, sem necessidade de agregação de dispositivos ou uso de tecnologias avançadas. Em 2011, Walker et al. realizaram um ECR avaliando a eficácia de ligações telefônicas periódicas com ênfase em educação em diabetes em pacientes com DM2 descompensado. Verificou-se um benefício a favor da intervenção, com uma diferença de HbA1c de 0,40% (95% CI 0,10–0,70, P=0.009) em relação ao controle. O benefício foi mais expressivo nos pacientes que recebiam a intervenção de forma mais intensiva (mais de 6 ligações em 12 meses de estudo) [24]. Em 2018, Dobler et al. também demonstraram, através de um ECR com

amostra de 249 pacientes com DM2, um benefício de ligações telefônicas com conteúdo educativo e estímulo a maior adesão ao tratamento no controle glicêmico (- 0,68% em HbA1c no grupo intervenção após 12 meses; p=0,006) [25]. De Vasconcelos et al. avaliaram a eficácia desta intervenção na população brasileira. Foram randomizados 36 pacientes com DM2 de uma unidade básica do Ceará em grupo intervenção (ligações telefônicas a cada 2 semanas por 6 meses com ênfase em educação em diabetes e estímulo a adesão) e controle (atendimento de rotina). Verificou-se uma redução numérica, mas estatisticamente não significativa na HbA1c do grupo intervenção (queda de 0,8%; p=0,052) [26]. Estes resultados já demonstram alguma evidência de benefício das ligações telefônicas no controle glicêmico, no entanto os estudos avaliados são bastante heterogêneos em termos da população estudada, duração e intensidade da intervenção. Também faltam dados mais robustos e focados na realidade brasileira.

Em 2005, o Ministério da Saúde do Brasil iniciou um projeto de implementação de núcleos de telemedicina em 9 estados do país. No ano de 2007, com apoio do Departamento de Epidemiologia da Universidade Federal do Rio Grande do Sul (UFRGS) foi criado o TelessaúdeRS. Desde 2013, o TelessaúdeRS vem realizando teleconsultas através de ligações telefônicas para auxílio a médicos da atenção primária de todo o país. As teleconsultas objetivam a resolução de casos clínicos na tentativa da redução da necessidade de encaminhamentos e consultas presenciais com especialistas de centros terciários [27]. De acordo com os últimos dados, estima-se que o TelessaúdeRS resolva cerca de 66% dos casos clínicos discutidos à distância, evitando o encaminhamento para a rede especializada em 2 a cada 3 ligações de consultoria [28]. Foram desenvolvidos, também, protocolos de encaminhamento com estratificação de risco dos pacientes com necessidade de serviço especializado. Em coorte retrospectivo publicado em 2020, Pfeil et al. demonstraram uma significativa redução no tempo de espera do paciente até a consulta com especialista, principalmente em pacientes considerados de alto risco, no grupo que teve sua referência mediada pelo TelessaúdeRS, em comparação ao controle [29]. Assim, o

TelessaúdeRS vem demonstrando-se uma promissora alternativa para melhora da resolutividade da APS e do acesso do paciente ao sistema público de saúde [30].

Referência/contrarreferência de pacientes com DM

Quanto ao processo de referência/contrarreferência de pacientes com DM, predominam na literatura informações de estudos sobre o referenciamento de pacientes da APS para os centros terciários [31]. No entanto, as evidências sobre a qualidade e as melhores formas de auxiliar o processo de contrarreferência (alta ambulatorial do serviço terciário para o primário) são escassas.

São apontadas como barreiras ao processo de transição do cuidado para a atenção primária: falta de comunicação com os especialistas para discussão de casos, falta de experiência dos médicos da atenção primária com insulinoterapia, ausência de confiança do paciente no médico de família e ausência de equipe multidisciplinar [32]. O fornecimento de um plano de cuidado na alta do centro especializado, orientando as metas do paciente e os tratamentos empregados, além de ferramentas que possam dar suporte ao autocuidado do paciente são possíveis alternativas para melhora da transição do cuidado.

O uso de estratégias em telemedicina como o TelessaudeRS através de ligações telefônicas de suporte pode auxiliar o processo de transição do cuidado do paciente com DM. Esta estratégia já foi testada em pacientes com cardiopatia isquêmica estável elegíveis para alta ambulatorial de serviço terciário [30], mas estudos que avaliem a sua efetividade no acompanhamento após alta de pacientes com DM2 ainda não estão disponíveis. Faz-se importante, portanto, determinar se ligações telefônicas são um instrumento eficaz na melhora do controle glicêmico do paciente com DM2 e se esta estratégia pode auxiliar o manejo do paciente na transição do cuidado, garantindo uma alta ambulatorial mais segura e consequentemente, uma redução da superlotação dos serviços terciários, permitindo que os

mesmos tratem casos mais raros e complexos, melhorando a acessibilidade e a alocação dos recursos públicos. Assim, essa tese tem dois objetivos:

- Avaliar a eficácia de ligações telefônicas no controle glicêmico dos pacientes com DM2 em comparação ao cuidado de rotina;

- Avaliar a eficácia de ligações telefônicas periódicas realizadas por enfermeiras no controle glicêmico, pressórico e lipídico dos pacientes com DM2 em comparação ao cuidado de rotina, assegurando a transição segura e de qualidade entre serviço especializado e atenção primária.

Referências Bibliográficas

[1] International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation, 2019. http://www.diabetesatlas.org

[2] A. Mirahmadizadeh, M. Fathalipour, A. Mohammad Mokhtari, S. Zeighami, S. Hassanipour, A. Heiran. (2019) The Prevalence of undiagnosed type 2 diabetes and prediabetes in Eastern Mediterranean Region (EMRO): a systematic review and meta-analysis. Diabetes Research and Clinical Practice 160:107931

[3] Zimmet P, Alberti KGMM, Shaw J. (2001) Global and societal implications of the diabetes epidemic. Nature 414:782-787

[4] Zheng Y, Ley SH, Hu FB. (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinology 14: 88-98

[5] Faselis C, Katsimardou A, Imprialos K et al. (2020) Microvascular Complications of Type 2 Diabetes Mellitus. Current Vascular Pharmacology 18: 117-124

[6] Zhang XX, Kong J, Yun K. (2020) Prevalence of diabetic nephropathy among patients with type 2 diabetes mellitus in China: a meta-analysis of observational studies. Journal of Diabetes Research; p 1 – 11

[7] Vaidya V, Gangan N, Sheehan J. (2015) Impact of cardiovascular complications among patients with Type 2 diabetes mellitus: a systematic review. Expert Rev. Pharmacoecon. Outcomes Res; p. 1-11

[8] Tacredi M, Rosengren A, Svensson A et al. (2015) Excess mortality among persons with Type 2 diabetes. N Engl J Med 373:1720-32.

[9] Gregg EW, Sattar N, Ali MK. (2016) The changing face of diabetes complications. Lancet Diabetes Endocrinol 4: 537–47

[10] Htay T, Soe K, Lopez-Perez A, Doan AH, Romagosa MA, Aung K. (2019) Mortality and cardiovascular disease in Type 1 and Type 2 diabetes. Current Cardiology Reports 21 (45): 1-7

[11] International Diabetes Federation. Global Diabetes Plan 2011-2021. Brussels, Belgium:

International Diabetes Federation, 2012

[12] Mudaliar U, Kim WC, Kirk K, Rouse C, Narayan KMV, Ali M. (2013) Are recommended standards for diabetes care met in Central and South America? A systematic review. Diabetes Research and Clinical Practice; p. 306-329

[13] Mendes EV. As redes de atenção à saúde. Brasília, Brasil: Organizacão Pan-Americana da Saúde, 2011

[14] Harzheim E, Gonçalves MR, Umpierre RN et al. (2016) Telehealth in Rio Grande do Sul, Brazil: bridging the gaps. Telemedicine and E-Health 22 (11): 1-7

[15] Liddy C, Afkham A, Drosinis P, Josch K, Keely E. (2015) Impact of and satisfaction with a new eConsult Service: a mixed methods study of primary care providers. J Am Board Fam Med 28:394–403

[16] Shwamm LH. (2014) Telehealth: Seven strategies to successfully implement disruptive technology and transform health care. Health Affairs 33 (2): 200-206

[17] Hayıroğlu MI. (2019) Telemedicine: current concepts and future perceptions. Anatol J Cardiol 22: 21-2

[18] American Diabetes Association. (2020) Improving care and promoting health in populations: Standards of Medical Care in Diabetes-2020. Diabetes Care 43(Suppl. 1): S7–S13

[19] Borries TM, Dunbar A, Bhukhen et al. (2019) The impact of telemedicine on patient self-management processes and clinical outcomes for patients with Types I or II Diabetes Mellitus in the United States: A scoping review. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13: 1353-1357

[20] Marcolino MS, Maia JX, Alkmin MBM, Boersma E, Ribeiro AL. (2013) Telemedicine application in the care of diabetes patients: Systematic Review and Meta-Analysis. Plos One 8 (11): 1-13

[21] So CF, Chung JWY. (2017) Telehealth for diabetes self-management in primary healthcare - a systematic review and meta-analysis. Journal of Telemedicine and Telecare 0(0):1-9

[22] Heitkemper EM, Mamykina L, Travers J, Smaldone A. (2017) Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. Journal of the American Medical Informatics Association 0(0): 1–13

[23] Lee PA, Greenfield G, Pappas Y. (2018) The impact of telehealth remote patient monitoring on glycemic control in type 2 diabetes: a systematic review and meta-analysis of systematic reviews of randomized controlled trials. BMC Health Services Research 18: 1-10

[24] Walker EA, Shmukler C, Ullman R et al. (2011) Results of a successful telephonic intervention to improve diabetes control in urban adults. Diabetes Care 34:2–7

[25] Dobler A, Pollmann H, Raspe H et al. (2018) Telephone-delivered lifestyle support with action planning and motivational interviewing techniques to improve rehabilitation outcomes. Rehabilitation Psychology 63(2): 170–181

[26] De Vasconcelos HCA, Neto JCGL, de Araújo MFM et al. (2018) Telecoaching programme for type 2 diabetes control: a randomised clinical trial. British Journal of Nursing, 27(19) : 1115-1120

[27] Gonçalves MR, Umpierre RN, D'Ávila OP et al. (2017) Expanding primary care access: a telehealth success story. Ann Fam Med 15(4):383

[28] Ministério da Saúde/Governo Federal do Brasil. Publicação eletrônica em Telessaúde – RS, 2020. Diponível no site < http:// www.ufrgs.br/telessauders/>. Acesso em 24 de outubro de 2020

[29] Pfeil JN, Rados DV, Roman R et al. (2020) A telemedicine strategy to reduce waiting lists and time to specialist care: A retrospective cohort study. Journal of Telemedicine and Telecare 0(0): 1–8

[30] Ruschel KB, Rados DV, Furtado MV et al. (2020) Transition of care of stable ischaemic heart disease patients from tertiary to primary care with telemedicine support: Randomized noninferiority clinical trial. Journal of Telemedicine and Telecare 0(0): 1–6

[31] Forrest C, Nutting P, von Schrader S, Rohde C, Starfield B. (2006) Primary care physician specialty referral decision making: patient, physician, and health care system determinants. Medical Decision Making 26(1):76-85.

[32] Brez S, Rowan M, Malcolm J et al. (2009) Transition from specialist to primary diabetes care: A qualitative study of perspectives of primary care physicians. BMC Family Practice 10 (39): 1-8

Capítulo 1

Effect of Telephone-calls on Glycemic Control in Type 2 Diabetes Mellitus Patients: a PRISMA- compliant Systematic Review and Meta-analysis with Trial Sequential Analysis

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ABSTRACT

Background: Telephone-calls can be a cost-effective telemedicine tool in type 2 diabetes (T2DM) management. In the last decades, it has been growing evidence evaluating its application, but in-depth and updated systematic reviews about this theme are missing. The objective of this meta-analysis was to assess the effect of telephone-call intervention in glycemic control of T2DM patients when compared to usual care.

Methods: Randomized controlled trials (RCT) of telephone intervention in T2DM were searched through Medline (Pubmed), Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and LILACS. Electronic search was done until August 2020. The following terms were used: diabetes mellitus, randomized controlled trials, telephone and telemonitoring. The trials quality was assessed using Risk of Bias 2.0 (Rob 2.0) tool and GRADE evaluation. Intervention effect was estimated with mean difference in glycated hemoglobin (HbA1c) change from baseline between intervention and control groups. PROSPERO registry CRD42020204519.

Results: In total, 2895 references were reviewed and 28 were included. Regarding the telephone-calls content, all studies approached T2DM education, and 6 of them also evaluated remote treatment modification. Telephone calls improved HbA1c in 0.34% [95% CI -0.5% to -0.17%; I^2 =80%; P <0.0001] compared to usual care. We did subgroup analysis with baseline HbA1c, treatment modification, professional involved in intervention and phone-calls frequency, but a high heterogeneity remained. A greater improvement was found when intervention included pharmacologic modification (-0.82%, 95% CI -1.42% to -0.22%; I^2 =92%), and when it was applied by nurses (-0.54%, 95% CI -0.9% to -0.18%; I^2 =88%). Meta-regression showed no relationship between disease duration and HbA1c changes.

Conclusion: Telephone-calls intervention has a statistically significant benefit in T2DM glycemic control, especially if associated with patient education and pharmacological modification.

However, the high heterogeneity level and the small effect on HbA1c limit our results and additional studies on this topic should approach more highly effective interventions.

INTRODUCTION

Currently, the use of telemedicine strategies in health care scenarios is a hotly debated topic. In the USA, at least 15% of physicians work in practices that use telemedicine [1]. As its adoption increases, it is expected to migrate and integrate with in-personal care [1]. Telemedicine is defined as the use of telecommunication and information technologies to support the delivery of health care at a distance [2]. There is growing investigation evaluating the use of telemedicine as an auxiliary in some chronic diseases' management, with a tendency of evidencing benefit, especially T2DM patients [3-6].

T2DM is a non-communicable disease with an increasing prevalence through the last decades. In 2019, it was estimated a DM global prevalence of 9.3% (463 million of people) [7], and T2DM was responsible for almost 90-95% of this statistic [8]. Besides that, according to American Diabetes Association (ADA) the proportion of DM adults that achieve glycemic targets is only 64% [9] and this data can be more disappointing in developing countries. A Brazilian cohort showed that only 33% of T2DM patients were on glycemic target [10]. Thus, developing strategies focused on patient care that facilitates the accessibility to DM management seems to be essential to improve this scenario.

Telemedicine use in T2DM is a promising and attractive field, and there is already some evidence of its application comparing or in addition to usual care [11-16]. It can be useful to improve glycemic control, especially in populations with limited accessibility to health care. In 2017, Faruque et al. evaluated through a meta-analysis of randomized controlled trials (RCT) the overall effect of telemedicine tools (videoconference, SMS, automated voice, telephone, web-portal, softwares) in DM patients' glycemic control. They found an improvement of 0.28% in glycated hemoglobin (HbA1c) in telemedicine groups [12]. Similarly, in 2018, Wu et al. through

a systematic review, found a reduction in HbA1c of 0.22%, favoring telemedicine interventions [13]. These systematic reviews analyzed telemedicine in general and did not focus specifically on any telemedicine tool. Considering that there are different telemedicine approaches, it turns difficult to generalize these results.

Telephone-calls can be a cost-effective alternative to improve glycemic control. In 2018, it was estimated that almost 93% of residences in Brazil had access to a cell phone, turning this tool more available than internet (79% of residences), especially in rural areas [17]. There is some evidence regarding the use of telephone-calls in T2DM management [18-23]. However, systematic reviews published until now showed variable effects on glycemic control [18], with a small number of studies, high heterogeneity level and lack of sensitive analysis [19].

Therefore, we conducted a systematic review and meta-analysis of RCTs to assess the effect of telephone-calls without electronic devices compared to usual care on T2DM patients' glycemic control.

METHODS

Study design and protocol

This study is a systematic review of RCT registered in Prospective Register of Systematic Reviews (PROSPERO) database under the number CRD42020204519 and followed Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [24].

Study eligibility criteria and search

The studies were eligible if they were RCT, evaluated the effects of telephone intervention compared to usual care to improve glycemic control measured as HbA1c (with or

without other aims) in patients with T2DM and lasted more than 12 weeks. Studies that evaluated other telemedicine tools (software, videoconference, short message, automated message, Bluetooth, mobile apps) were excluded. Trials that used other telemedicine intervention as a comparator were also excluded. There were no restrictions regarding language. We searched Pubmed, Embase, Cochrane Central, LILACS and CINAHL databases. No date restrictions were included; last search update was August 11th 2020. Search main terms were: *diabetes mellitus* AND *telephone* OR *telemonitoring* and filters for RCTs. Search strategy and RCT filters used are detailed in Supplemental Material (Supplementary 1).

Study selection

Two researchers (AMM and RM) performed studies selection and data extraction in duplicate. Disagreements were solved by consensus; if disagreement remained, another researcher (SPS) resolved it. First, titles and abstracts were screened and selected according to the eligibility criteria mentioned above. After screening, the selected studies were reviewed in full text for eligibility. Studies were included in this systematic review and meta-analysis if inclusion criteria were fulfilled and outcomes of interest were analyzed.

Data collection

Data was extracted in electronic database and in duplicate. The following information was extracted from the included articles: study and publication characteristics (author full-name, publication year, title, country, number of patients included, study duration), patients' information (selection criteria, age, sex), intervention information (telephone-calls content and frequency, professional responsible for intervention) and outcomes data (HbA1c mean and standard deviation at baseline and end of study and number of participants analyzed in both groups). Missing outcomes were searched in clinicaltrials.org registry or by direct contact with authors.

Risk of bias assessment

We evaluated bias in individual studies with Cochrane´s "Risk of Bias 2.0" tool. The quality of evidence for each outcome with the GRADE approach as "high", "moderate", "low", and "very low" [25]. Factors involved in the quality of the results of the meta-analysis were risk of bias (methodologic limitations) of individual studies, inconsistency, indirectness of evidence, imprecision, small-study bias, magnitude of effect, dose-response gradient, and residual confusion bias.

Data analysis

To examine the overall magnitude of effect in using phone-calls intervention as a tool to improve HbA1c in T2DM patients, we conducted a conventional pairwise meta-analysis of the included RCT. Furthermore, we stratified this analysis according to baseline HbA1c (using HbA1c value of 8% as a cut point), professional who applied intervention (nurse, pharmacist or diabetes educator), if medication and dosing adjustments was part of the intervention, and according to intervention frequency (using twice a month as a cut point). For the main outcome (HbA1c), weighted mean differences were used with inverse variance methods. We chose random-effects model due to intervention heterogeneity (different approaches in telephone-calls intervention). To assess the analysis' statistical heterogeneity, we performed Cochran's Q and the I^2 test. A *p*-value <0.1 and an I^2 >50% were considered as elevated heterogeneity, respectively. A funnel plot generated in Review Manager 5.4 (RevMan 5.4) for HbA1c was used to visually assess small-study bias, and asymmetry was tested with Begg and Egger tests in R statistics software. If small-study bias was suspected, the trim-and-fill computation was planned to evaluate the effects of missing studies on the analysis. We also performed a trial sequential analysis (TSA) that created a cumulative meta-analysis (represented by the Z-curve) and boundaries for futility, benefit, and harm; if the curve crosses one of the boundaries, or reaches the optimal sample size line,

definitive conclusion can be assumed. The conventional pairwise meta-analyses were conducted with reference to the Cochrane Handbook for Systematic Reviews [25]. We performed meta-analyses with Review Manager 5.4 (RevMan 5.4).

RESULTS

Search results, study characteristics and risk of bias

Study selection process is presented in Figure 1. In summary, 2895 references were located, 2205 titles and abstracts were screened, remaining 100 articles for full-text review. The main exclusion reasons were application of other electronic intervention besides telephone-calls (36 studies) and missing outcome data (11 studies). Finally, 28 studies were selected for systematic review, a total of 7952 patients (4033 in intervention and 3919 in control group).

The characteristics of included studies are shown in Table 1. The individual trials sample varied from 35 to 1400 patients. O´ Connor et al. divided their sample in 3 subgroups (patients with baseline uncontrolled HbA1c, LDL-cholesterol and systolic blood pressure), we included in our analysis only the subgroup that presented glycemic control data (patients with baseline uncontrolled HbA1c). Our systematic review found a mean age range from 50 to 70 years-old, with female gender predominance (almost 60%). Studies lasted from 12 to 96 weeks. The intervention in all evaluated studies was focused in T2DM education, adherence improvement, self-care management, aiming the improvement of the understanding of patients about T2DM. Of all 28 included studies, 6 also made pharmacological treatment changes or titration.

Regarding intervention intensity (phone-calls frequency), there was a great variability. While some studies adopted a weekly frequency, others called patients according to their risks, and others applied intervention monthly or over wider periods. In most studies, nurses were

involved in telephone-calls. Two studies had more than one intervention group. Dale J et al. presented 2 intervention groups, according to the person responsible for telephone-calls (nurses or peer-supporters). We decided to prioritize the intervention application by health care professionals, so only the nurse group was included in analysis. Egede et al. showed 3 intervention groups based on different levels of T2DM education (skills only, knowledge only or skills and knowledge in combination). We included the more complete approach (skills and knowledge combined) in the analysis. Regarding the risk of bias, most studies were classified as low risk (Supplementary Fig 5 and 6).

Efficacy on glycemic control

Twenty-eight studies contributed to meta-analysis of the primary outcome. Telephone intervention significantly improved glycemic control (HbA1c) when compared to usual care (pooled mean difference -0.34%, 95% CI -0.5% to -0.17%), with a high level of statistical heterogeneity (I^2 =80%; p < 0.0001) (Figure 2).

As pre-specified, we performed some subgroup analysis. High heterogeneity persisted even when we stratified to baseline glycemic control (Suppl. Figure 1) and frequency of phone-calls (Suppl. Figure 2). Telephone calls that associated education with pharmacological modification seem to have a greater effect (pooled mean difference -0.82%, 95% CI -1.42% to -0.22%), but with a significant heterogeneity (I^2 =92%; p < 0.0001) (Figure 3).

Regarding the professional responsible for intervention, studies conducted by DM educators or coaches had a non-significant decrease in HbA1c (pooled mean difference -0.12%, 95% CI -0.31% to 0.06%) with a non-significant heterogeneity (I^2 =22%; p=0.27) (Figure 6). When intervention was applied by other professionals (nurses and pharmacists), the high level of heterogeneity persisted (Figure 4 and 5). Phone-calls intervention done by nurses had a more expressive HbA1c decrease (-0.54%, 95% CI -0.9% to -0.18%) (Figure 4). Meta-regression was

performed to assess a possible correlation between HbA1c and disease duration, but no relationship was found (Supplementary Fig 3). Funnel-plot was performed, and no small-study bias was observed (Begg and Egger tests not significant) (Supplementary Fig 4). TSA was performed to assess the statistical power of our meta-analysis results. Z-curve reached benefit boundary, confirming our results. Furthermore, TSA shows that a sample size of 1700 patients is necessary to reach a clinically significant change in glycemic control (stablished as a decrement of 0.5% in HbA1c). This confirms that our meta-analysis had sufficient power to identify this difference between groups. (Supplementary Fig 7).

GRADE evaluation

For all outcomes, the quality of evidence was considered moderate (Summary of findings table - Suppl. Figure 8). Even though data was based on RCTs data (high quality), a 1-point downgrading was applied due to inconsistency (high heterogeneity – both clinical and statistical). Remaining factors were adequate: risk of bias from studies was considered low, no indirect evidence, confidence intervals were not excessively wide, and no small-study biases were observed in Funnel-Plot.

DISCUSSION

Our meta-analysis included 28 trials and a large sample size (7952 patients) and showed that periodically telephone-calls had a significant benefit in T2DM patients' glycemic control compared to usual care with a moderate evidence quality. In all included studies, the phone-calls content was focused on T2DM education (adherence, diet, exercise, foot care and lifestyle improvement). Only 6 studies approached T2DM pharmacologic modification, and these ones achieved a considerably greater improvement in glycemic control. Furthermore, when

intervention was applied by nurses (14 studies), a greater HbA1c decrease was reached compared to other health professionals.

We focused on one specific telemedicine intervention (telephone-calls) and a single condition (T2DM) was evaluated. It allowed us to generate applicable and relevant information. Telemedicine is a wide expression and systematic reviews that already explored it included mixed interventions (videoconference, SMS, software, Bluetooth data transmission, telephone, mobile apps) [12,13,26] and heterogeneous population (T2DM and T1DM) [11,15], turning difficult to analyze their results individually. Regarding the content of our evaluated intervention, all studies approached T2DM education and improvement of patient self-care. According to American Diabetes Association recommendations, diabetes self-management education is necessary for optimal diabetes care with solid evidence of benefit [27-30]. Other strengths of our study were the large number of analyzed studies leading to a great sample size, and a wide search strategy through 5 different databases. We also did a robust analysis of our findings. Heterogeneity level was explored through different subgroup analysis and meta-regression was done to assess discrepancies. Furthermore, to reaffirm and empower our results, we did a Trial Sequential Analysis.

Some limitations from our study must be discussed. We controlled the clinical heterogeneity of the large group of "Telemedicine" interventions by selecting only one kind of intervention (telephone-based) by health-care professionals. However, we found a high level of statistical heterogeneity. It was explored with subgroup analysis according to basal HbA1c levels, treatment modification, professional involved in the intervention, and phone-calls frequency, but the high heterogeneity remained. We also did a meta-regression with diabetes duration and found no relationship. It may be explained by differences between included studies regarding population characteristics and adherence, sample size and usual care approach but our data do not allow such analysis. Second, regarding the clinical relevance of our findings, we have some

concerns. Indeed, as recent published by McCormack and Holmes, the aggregated analytical and biological variation of HbA1c method can reach 10 to 20% [31]. Besides that, according to the "National Glycohemoglobin Standardization Program (NGSP)", a relative change in HbA1c value less than 6.8% from baseline is within the estimated laboratory variation coefficient and cannot be considered clinically relevant [32].

Our results are in accordance with previous systematic reviews aimed to evaluate the telemedicine effect on DM management [16, 33]. In 2018, Lee et al. showed a benefit of telemedicine strategies on glycemic control compared to usual care (HbA1c reduction in 0.55%; 95% CI -0.73% to -0.36%). When stratified to telemedicine strategy applied, telephone-calls achieved a greater improvement in HbA1c (- 0.88%, 95% CI -1.54% to 0.12%; $I^2$86%) [16]. In 2017, Lee et al. showed that teleconsultation and telemonitoring were both effective in HbA1c improvement [33]. However, these systematic reviews were not aimed to evaluate telephone-calls as the main intervention, only assessed its efficacy in glycemic control though subgroup analysis.

Our findings disagree with a previous meta-analysis designed to assess the effect of phone-calls intervention in DM glycemic control. They reported no significant benefit in HbA1c (-0.38% 95% CI -0.91 to -0.16; I^2 85%) [19]. However, their results are limited due to the small amount of included studies and the absence of subgroup analysis that did not allow an exploration of the high heterogeneity levels [19]. Our systematic review studied a largely available telemedicine tool with a potential clinical benefit in T2DM, highlighting the clinical relevance of this report and improving the knowledge in a growing research field. To further strengthen the current evidence about this topic, future reviews should also consider addressing other outcomes such as cost-effectiveness and quality of care.

In conclusion, our meta-analysis showed that health-care personnel lead phone-calls intervention improves glycemic control in patients with T2DM. However, due to the heterogeneity and small effect on HbA1c, our results must be evaluated with caution. Additional studies on this topic must focus on more highly effective interventions that might provide greater (i.e. clinically significant) HbA1c reduction.

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Author contributions

AMM was responsible for study design, data acquisition, analysis, interpretation, and drafting of the manuscript. RM contributed to study design, reference selection, and data acquisition. GE contributed to data analysis and interpretation. DVR contributed to study design, data analysis and interpretation, and drafting of the manuscript. SPS contributed to study design, analysis, interpretation, and drafting of the manuscript. All authors have read and approved the final manuscript. AMM is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

Support for the English review was provided. FIPE-HCPA had no role in the design and conduct of the study; extraction, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Ethical approval

Not needed - exempted.

Conflict of interests

All authors have completed the ICMJE uniform disclosure form www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

Fig 1. PRISMA flow diagram

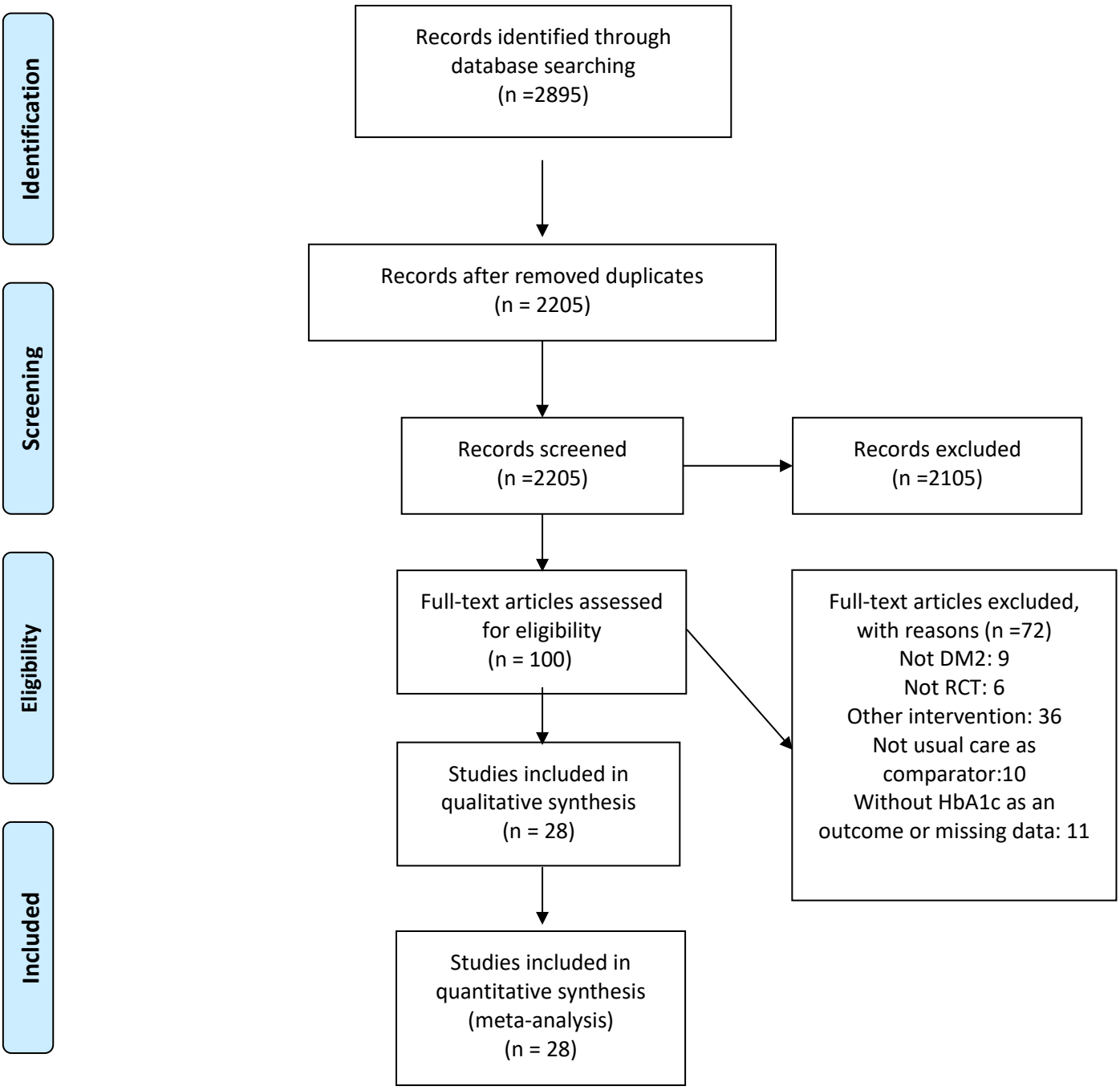


Table 1. Studies characteristics

Author	Year	Intervention	Intervention frequency	Mean age (years)	Gender (% female)	Follow-up (weeks)	Patients	HbA1c difference from baseline in intervention	HbA1c difference from baseline in control	Professional responsible for intervention
Anderson DR [34]	2010	Phone-calls approaching self-care, lifestyle, medical adherence and SMBG plus print material	According to patient risk: weekly, biweekly, or monthly	NA	58	48	295	0	-0.7	Nurses
Blackberry ID [35]	2013	Phone-calls focused on self-care improvement and treatment modification if needed	8 phone calls + 1 face-to-face visit	NA	NA	72	473	-0.1	-0.2	Nurses
Bluml BM [36]	2019	Diabetes Self-Management Education Program + Support phone-calls focusing on T2DM education	Biweekly on first 3 months and monthly after that	54	60	48	446	-1.7	-1.4	DM educators
Chan JCN [37]	2014	JADE portal (self-care reminders + alerts for treatment intensification for physician) + phone-calls focused in T2DM education	Biweekly on first 3 months, monthly for 3 months more and every 2 months for 6 months	54	46	48	628	-0.3	-0.3	DM educators
Chiu CJ [38]	2016	Phone-calls focused in understand patients' feelings and search solutions with improvements in lifestyle	3 or 4 phone-calls in 6 weeks	64	48	32	182	-0.1	-0.2	Nurses and psychologists
Clifford RM [39]	2005	Phone-calls focused in T2DM pharmacotherapy and lifestyle + newsletter	Every 6 weeks	70	48	48	198	-0.5	0	Pharmacists
Dale J [40]	2008	Phone-calls focused in T2DM education	5 phone-calls in 150 days	NA	45	24	231	-1.0	-0.8	Nurses

Author	Year	Intervention	Intervention frequency	Mean age (years)	Gender (%female)	Follow-up (weeks)	Patients	HbA1c difference from baseline in intervention	HbA1c difference from baseline in control	Professional responsible for intervention
De Vasconcelos HCA [41]	2018	Phone-calls focused in T2DM education	Biweekly	60	77	24	36	-0.8	+0.4	Nurses
Dobler A [42]	2018	Phone-calls focused in T2DM education and depression symptoms identification (PHQ scores)	Monthly	52	60	48	249	-0.7	+0.1	Nurses
Doupis J [43]	2019	Phone-calls focused in T2DM education and lifestyle modification + printed material	Biweekly	62	43	32	457	-1.0	-0.8	Physicians
Edelman D [44]	2015	Phone-calls focused on lifestyle improvement, medical adherence, and barriers to achieve hypertension and T2DM targets	Every 2 months	59	55	96	377	-0.6	-0.5	Nurses
Egede LE [45]	2017	Phone-calls with different content for 3 groups (skills only, knowledge only and skills and knowledge combined) all focused on lifestyle improvement, medication adherence and disease comprehension	Weekly for 12 weeks	53	44	48	255	-0.7	-1.1	DM educators
Estey AL [46]	1990	Phone-calls focused in T2DM education, SMBG and medication adherence	4 phone-calls in 3 months	56	55	12	60	-0.7	-0.3	Nurses
Kim HS [47]	2003	Phone-calls focused in T2DM education, incentive SMBG realization 2 times a	2 times a week for the first month, then weekly for 2 months	60	72	12	50	-1.2	+0.6	Nurses

		day and change in medication								
Author	**Year**	**Intervention**	**Intervention frequency**	**Mean age (years)**	**Gender (%female)**	**Follow-up (weeks)**	**Patients**	**HbA1c difference from baseline in intervention**	**HbA1c difference from baseline in control**	**Professional responsible for intervention**
Kim HS [48]	2005	Phone-calls focused in T2DM education, incentive SMBG realization 2 times a day and change in medication	2 times a week for the first month, then weekly for 2 months	61	64	12	35	-1.2	+0.6	Nurses
Lange I [49]	2010	Phone-calls focused in T2DM education, lifestyle improvement and footcare	13 phone-calls during study-period	50	67	60	640	+0.2	+1.4	Nurses
Lauffenburger JC [50]	2019	Phone-calls focused in T2DM education, lifestyle improvement, medical adherence with change in treatment	NA	54	37	48	1400	-0.8	-0.8	Pharmacists
Mons U [51]	2013	Phone-calls for understanding possible treatment barriers, lifestyle, and adherence improvement	Monthly	68	38	72	204	-0.3	-0.5	Nurses
Naik AD [52]	2019	Phone-calls focused on understanding patients' feelings and incentive activities for well-being and improvement in T2DM treatment	Biweekly for 3 months and monthly until 6 months	61	10	48	225	-0.5	-0.4	Nurses, psychologists, pharmacists, and social worker
Nesari M [53]	2010	Phone-calls focused in T2DM education, medical adherence and treatment change for an endocrinologist if necessary	2 times-a-week for 1 month and weekly for other 2 months	52	71	12	61	-1.86	-1.0	Nurses

Author	Year	Intervention	Intervention frequency	Mean age (years)	Gender (%female)	Follow-up (weeks)	Patients	HbA1c difference from baseline in intervention	HbA1c difference from baseline in control	Professional responsible for intervention
Oh J [54]	2003	Phone-calls focused in T2DM education, incentive SMBG realization 2 times a day and change in medication	2 times a week for the first month, then weekly for 2 months	60	64	12	50	-0.4	+0.6	Nurses
O'Connor PJ [55]	2014	Phone-calls after new drug introduction with emphasis in adherence improvement	Phone-call after 6 weeks of a medication change	62	52	24	1102	-1.1	-0.9	DM educators and pharmacists
Safford MM [56]	2015	Phone-calls as an auxiliary to achieve T2DM targets	Weekly for the first 2 months, and monthly for next 8 months	60	75	40	424	-0.1	0	DM educators
Sarayani A [57]	2018	Phone-calls focused in solve medication problems, discuss glycemic targets and reference to a doctor if necessary	2 times-a-week for the first month, and weekly for next 2 months	53	41	36	100	-1.0	-0.8	Pharmacists
Varney JE [58]	2014	Phone-calls focused on diet, exercise, treatment review, and self-care	Monthly	60	68	48	94	-0.8	+0.2	Dietician
Walker EA [59]	2011	Phone-calls focused in T2DM education	Every 4-6 weeks	55	67	48	526	-0.3	+0.1	DM educators
Weinberger M [60]	1995	Phone-calls focused in T2DM education, treatment review, adherence and facilitate	Monthly	64	1	48	275	-0.2	+0.4	Nurses

		communication with family physician								
Author	**Year**	**Intervention**	**Intervention frequency**	**Mean age (years)**	**Gender (%female)**	**Follow-up (weeks)**	**Patients**	**HbA1c difference from baseline in intervention**	**HbA1c difference from baseline in control**	**Professional responsible for intervention**
Wolever RQ [61]	2010	Phone-calls for a better T2DM understanding, comprehension of patient life goals and satisfaction	Weekly for first 2 months, biweekly in next 2 months and monthly until 6 months	53	77	24	56	-0.2	0	DM educators

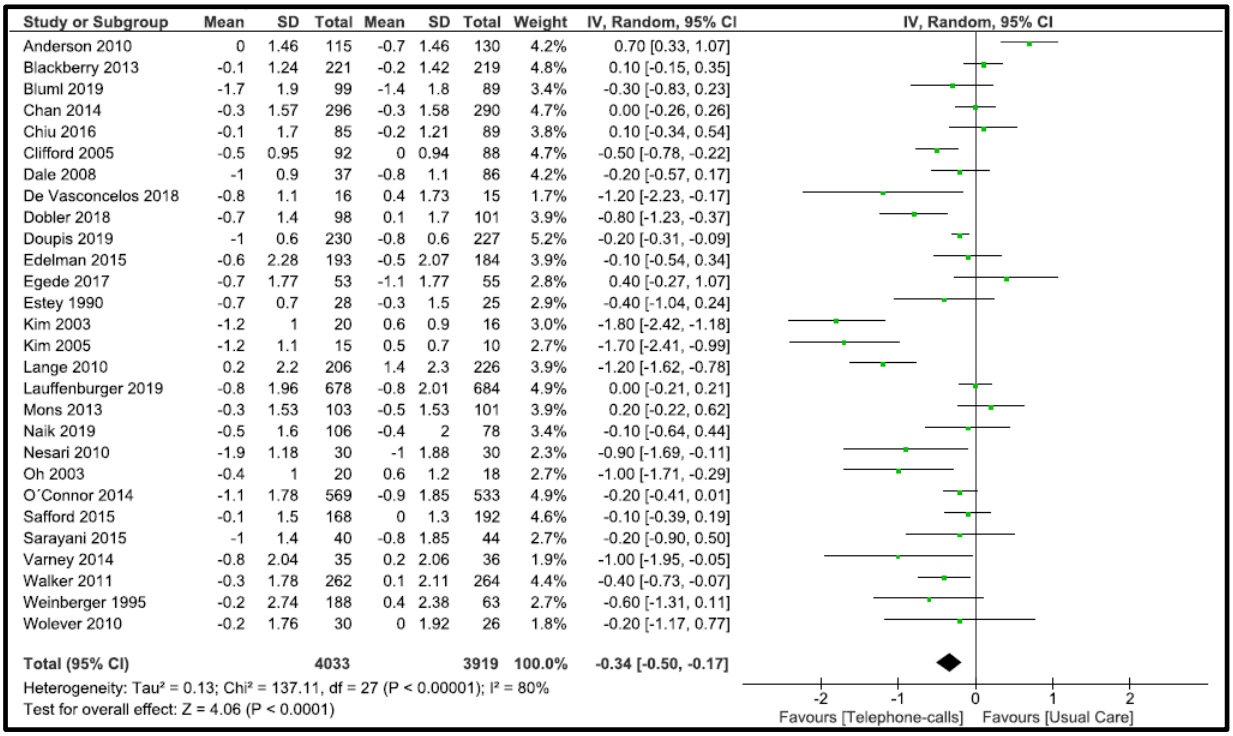


Fig. 2: Forest plot: overall effect of telephone-intervention in HbA1c levels.

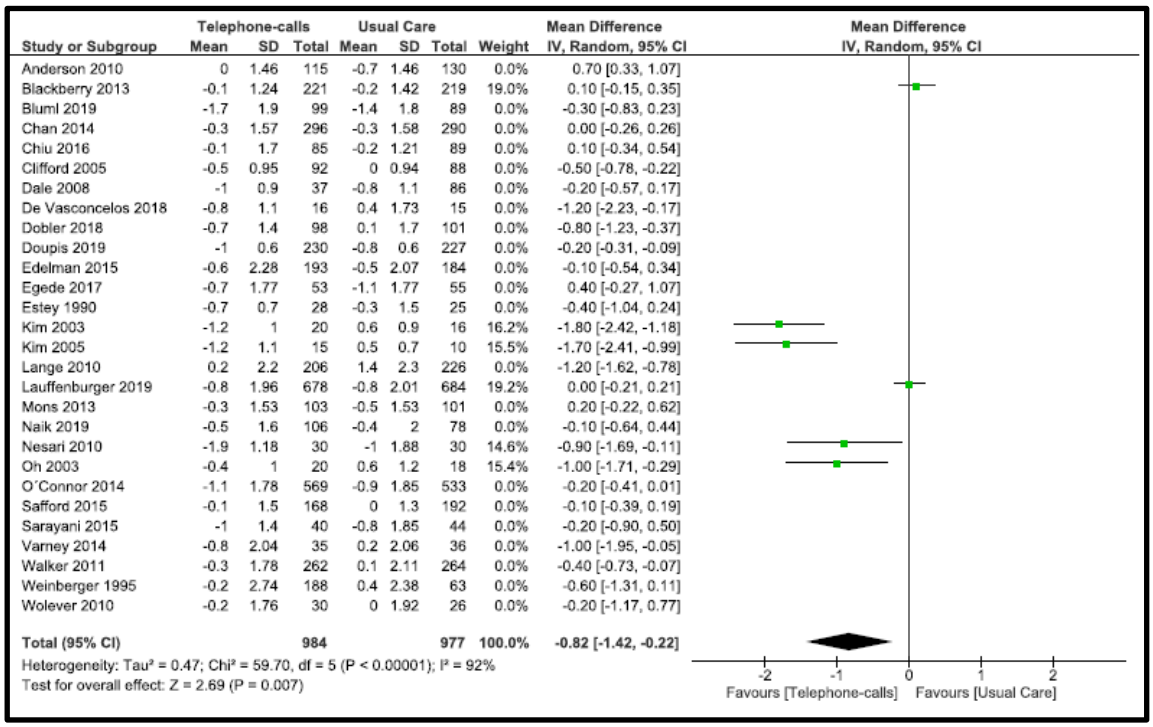


Fig 3: Forest plot (subgroup analysis) - studies presented intervention with T2DM treatment modification.

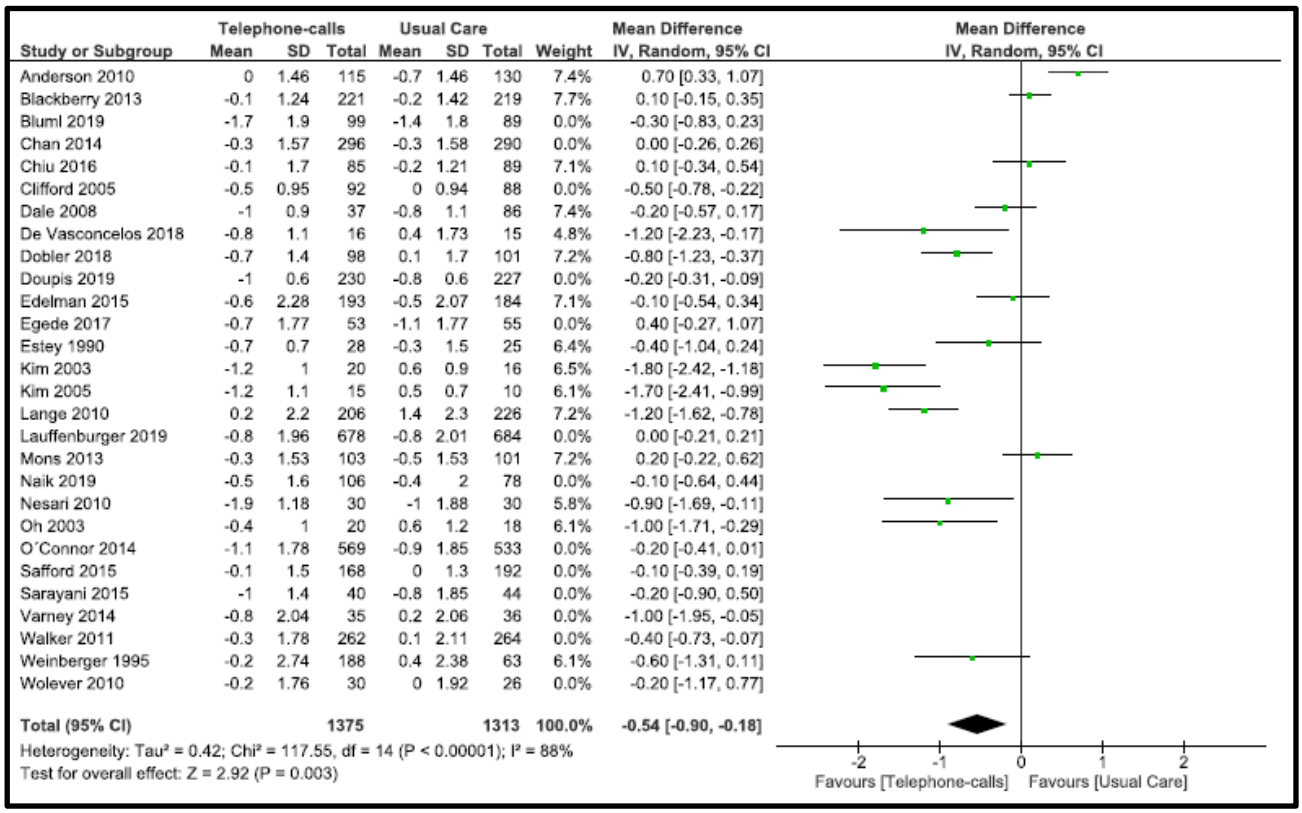


Fig 4: Forest plot (subgroup analysis) – studies with intervention applied by nurses

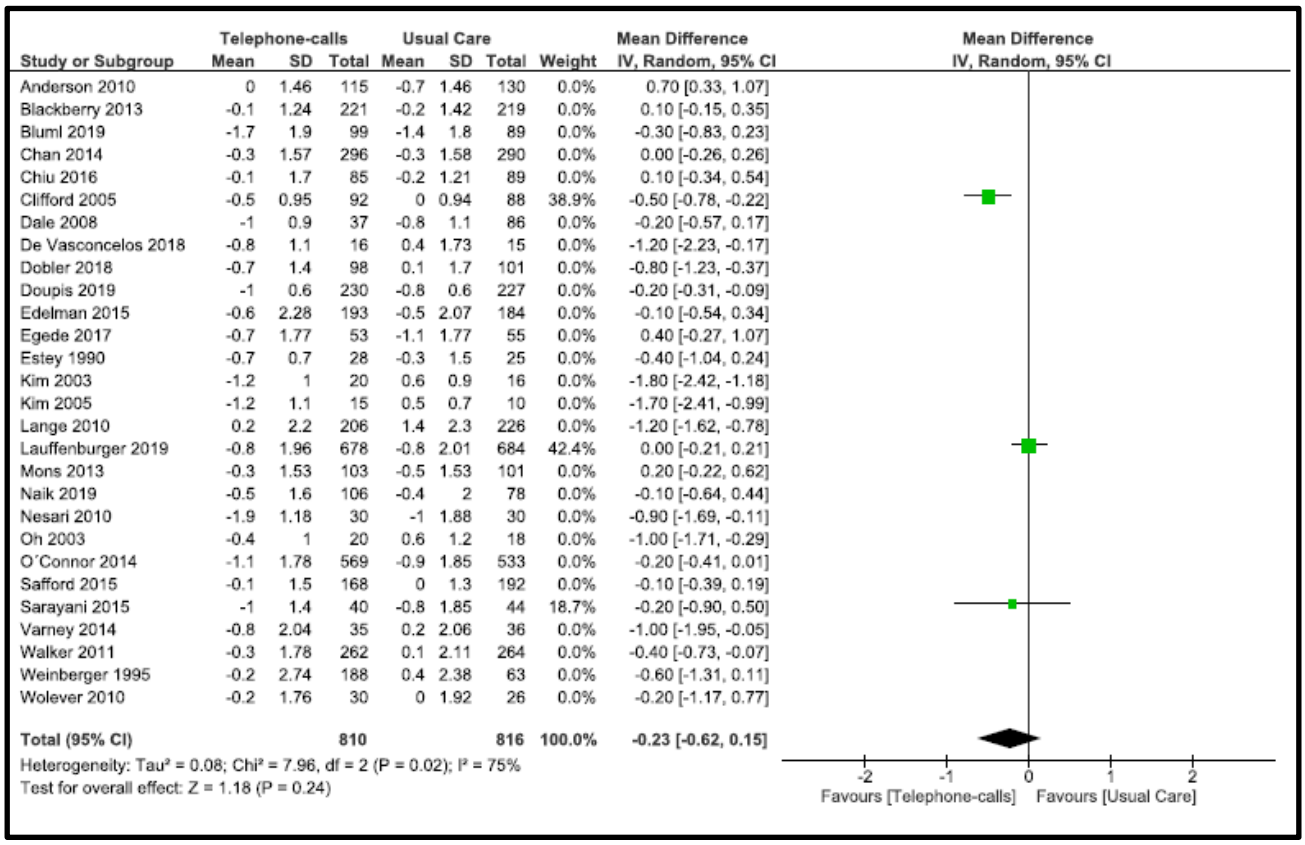


Fig 5: Forest plot (subgroup analysis) – studies with intervention applied by pharmacists

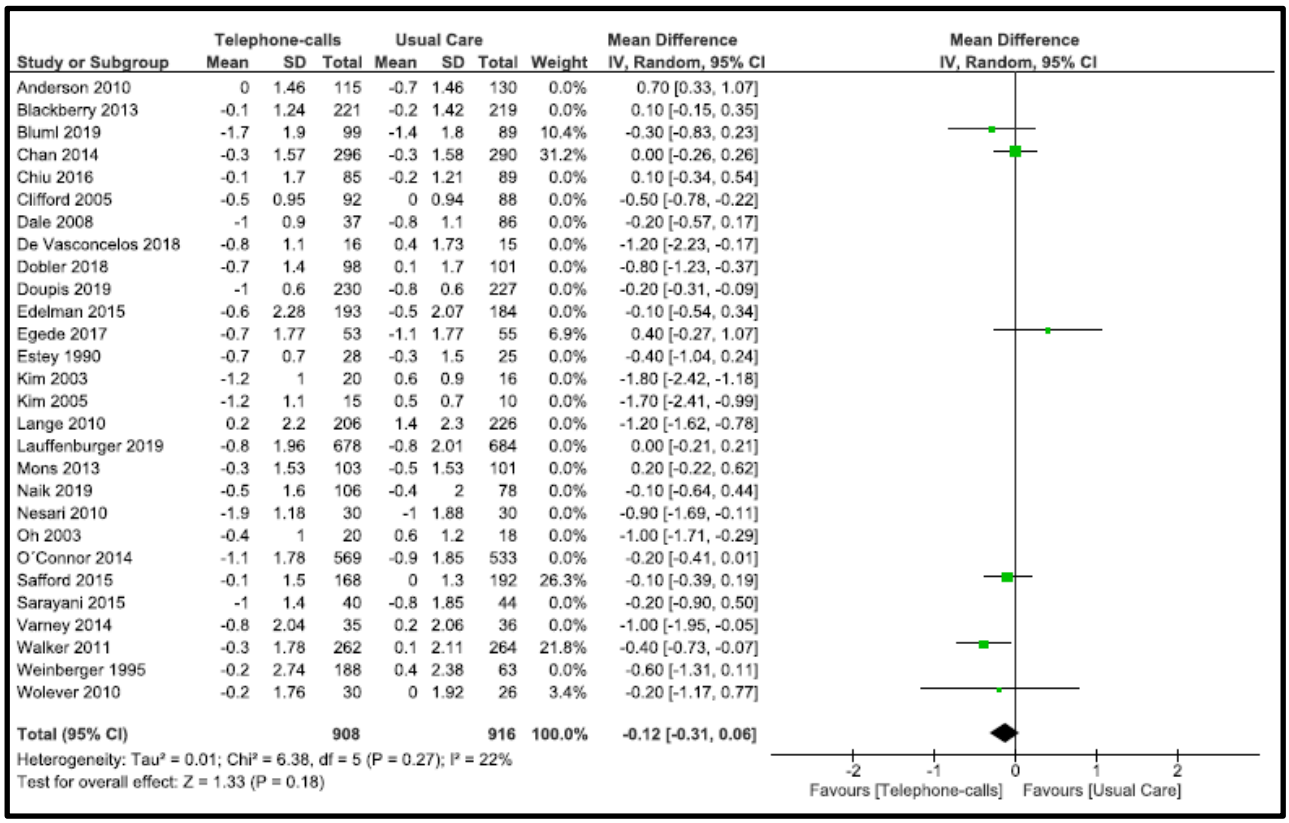


Fig 6: Forest plot (subgroup analysis) – studies with intervention applied by DM educators

References

[1] Dorsey ER, Topol EJ. (2020) Digital Medicine – Telemedicine 2020 and the next decade. Lancet 395: 859

[2] Eisenstein E, Kopacek C, Cavalcante SS, Neves AC, Fraga GP, Messina LA. (2020) Telemedicine: a bridge over knowledge gaps in healthcare. Current Pediatrics Reports p. 1-6

[3] Timpel P, Oswald S, Schwarz P, Harst L. (2020) Mapping the evidence on the effectiveness of telemedicine interventions in diabetes, dyslipidemia, and hypertension: an umbrella review of systematic reviews and meta-analyses. Journal of medical Internet research 22(3), e16791.

[4] Lunde P, Nilsson B B, Bergland A, Kværner K J, Bye A. (2018) The effectiveness of smartphone apps for lifestyle improvement in noncommunicable diseases: systematic review and meta-analyses. Journal of medical Internet research 20(5), e162

[5] Orozco-Beltran D, Sánchez-Molla M, Sanchez J J, Mira J J, ValCrònic Research Group. (2017) telemedicine in primary care for patients with chronic conditions: The ValCrònic Quasi-Experimental Study. Journal of medical Internet research 19(12), e400.

[6] Hanlon P, Daines L, Campbell C, McKinstry B, Weller D, Pinnock H. (2017) Telehealth interventions to support self-management of long-term conditions: a systematic metareview of diabetes, heart failure, asthma, chronic obstructive pulmonary disease, and cancer. Journal of medical Internet research19(5), e172.

[7] Saeedi P, Petersohn I, Salpea P et al. (2019) Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice 157:107843

[8] American Diabetes Association. (2020) classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 43(Suppl. 1): S14–S31

[9] American Diabetes Association. (2020) Improving Care and Promoting Health in Populations: Standards of Medical Care in Diabetes-2020. Diabetes Care 43(Suppl. 1): S7–S13

[10] Farias CB, Coelli S, Satler F, Brondani L, Zelmanovitz T, Silveiro SP. (2020) HbA1c and Blood Pressure Levels in Type 2 Diabetes: How many patients are on target? Canadian Journal of Diabetes DOI: https://doi.org/10.1016/j.jcjd.2020.10.002

[11] Greenwood DA, Gee PM, Fatkin KJ, Peeples M. (2017) A systematic review of reviews evaluating technology-enabled diabetes self-management education and support. Journal of Diabetes Science and Technology 11(5) 1015–1027

[12] Faruque LI, Wiebe N, Ehteshami-Afshar A et al. (2017) Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials. CMAJ 189: E341-64

[13] Wu C, Wu Z, Yang L et al. (2018) Evaluation of the clinical outcomes of telehealth for managing diabetes A PRISMA-compliant meta-analysis. Medicine (Baltimore) 97(43):e12962

[14] Haider R, Sudini L, Chow CK, Cheung W. (2019) Mobile Phone Text Messaging in Improving Glycaemic Control for Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Diabetes Res Clin Pract 150:27-37

[15] Tchero H, Kamgambega P, Briatte C, Brunet-Houdard S, Retali GR, Rusch E. (2018) Clinical Effectiveness of Telemedicine in Diabetes Mellitus: A Meta-Analysis of 42 Randomized Controlled Trials. Telemed J E Health 25(7):569-583

[16] Lee, PA; Greenfield, G; Pappas, Y. (2018) The impact of telehealth remote patient monitoring on glycemic control in type 2 diabetes: a systematic review and meta-analysis of systematic reviews of randomized controlled trials. BMC Health Services Research 18: 1-10

[17] Instituto Brasileiro de Geografia e Estatística (IBGE). (2018) Publicação eletrônica: Uso de Internet, Televisão e Celular no Brasil. Available in <educa.ibge.gov.br>. Last access November 3rd, 2020

[18] Graziano JA and Gross CR. (2009) The Effects of Isolated Telephone Interventions on Glycemic Control in Type 2 Diabetes - A Literature Review. Advances in Nursing Science 32 (3):

E28–E41

[19] Suksomboon N, Poolsup N, Nge YL. (2014) Impact of Phone Call Intervention on Glycemic Control in Diabetes Patients: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. PlosOne 9 (2):1-7

[20] Kaur R, Kajal KS, Kaur A, Sing P. (2015) Telephonic Consultation and follow-up in Diabetics: Impact on Metabolic Profile, Quality of Life, and Patient Compliance. North American Journal of Medical Sciences 7 (5): 199-207

[21] Trief PM, Fisher L, Sandberg J et al. (2016) Health and Psychosocial Outcomes of a Telephonic Couples Behavior Change Intervention in Patients with Poorly Controlled Type 2 Diabetes: A Randomized Clinical Trial. Diabetes Care 9: 2165-73

[22] Odnoletkova I, Goderis G, Nobels F et al. (2016) Optimizing diabetes control in people with Type 2 diabetes through nurse-led telecoaching. Diabet Med 33: 777-785

[23] Davidson MB, Davidson SJ. (2019) Effect of Remote Glucose Monitoring Utilizing Computerized Insulin Dose Ajustment Algorithms: A Pilot Project. Diabetes Ther, 10: 523–533.

[24] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med 6(7): e1000100.

[25] Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration

[26] Hangaard S, Laursen SH, Udsen FW, Vestergaard P, Hejlesen O. (2020) Telemedicine Interventions for the Management of Diabetes: A Systematic Review and Meta-Analysis. Stud Health Technol Inform 270:1403-1404

[27] American Diabetes Association. (2020) Facilitating Behavior Change and Well-being to Improve Health Outcomes - 2020. Diabetes Care 43(Suppl. 1): S48–S65

[28] Powers MA, Bardsley J, Cypress M et al. (2015) Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. Diabetes Care 38(7): 1372-1382

[29] Chrvala CA, Sherr D, Lipman RD. (2016) Diabetes self-management education for adults with type 2 diabetes mellitus: A systematic review of the effect on glycemic control. Patient Education and Counseling 99: 926–943

[30] He X, Li J, Wang B et al. (2016) Diabetes self-management education reduces risk of all-cause mortality in type 2 diabetes patients: a systematic review and meta-analysis. Endocrine 55(3):712-731

[31] McCormack JP and Holmes DT. (2020) Your results may vary: the imprecision of medical Measurements. BMJ 368: 1-5

[32] European Federation of Clinical Chemistry and Laboratory Medicine. Electronic publication in: EFLM, 2018. Available at < https://biologicalvariation.eu/>. Last access in November 2020

[33] Lee SWH, Chan CKY, Chua SS, Chaiyakunapruk N. (2017) Comparative effectiveness of telemedicine strategies on type 2 diabetes management: A systematic review and network meta-analysis. Sci Rep 7(1):12680

[34] Anderson D R, Christison-Lagay J, Villagra V, Liu H, Dziura. (2010) Managing the space between visits: a randomized trial of disease management for diabetes in a community health center. J Gen Intern Med **25**(10): 1116-1122

[35] Blackberry I D, Furler JS, Best JD et al. (2013) Effectiveness of general practice based, practice nurse led telephone coaching on glycaemic control of type 2 diabetes: the Patient Engagement and Coaching for Health (PEACH) pragmatic cluster randomised controlled trial. BMJ Clinical research 347: f5272

[36] Bluml B M, Kolb LE, Lipman R (2019). Evaluating the impact of year-long, augmented diabetes self-management support. Population health management 22(6): 522-528.

[37] Chan J C, Oldenburg B, Zhang Y et al. (2014) Effects of telephone-based peer support in patients with type 2 diabetes mellitus receiving integrated care: a randomized clinical trial. JAMA internal medicine 174(6): 972-981.

[38] Chiu C J, Hu Y, Wray LA et al. (2016) Dissemination of evidence-base minimal psychological intervention for diabetes management in Taiwan adults with type 2 diabetes. International journal of clinical and experimental medicine 9(7): 14489-14498

[39] Clifford, R M, Davis WA, Batty KT, Davis T. (2005) Effect of a pharmaceutical care program on vascular risk factors in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 28(4): 771-776

[40] Dale J, Caramlau I, Sturt J, Friede T, Walker R. (2009) Telephone peer-delivered intervention for diabetes motivation and support: the telecare exploratory RCT. Patient Educ Couns 75(1): 91-98

[41] de Vasconcelos H C A, Neto JCGL, de Araújo M et al. (2018) Telecoaching programme for type 2 diabetes control: a randomised clinical trial British Journal of Nursing 27(19): 1115-1120

[42] Dobler A, Pollmann H, Raspe H, Belnap B, Farin E, Mittag O. (2018) Telephone-delivered lifestyle support with action planning and motivational interviewing techniques to improve rehabilitation outcomes. Rehabilitation psychology 63(2): 170-181

[43] Doupis J, Alexandrides T, Elisaf M et al. (2019) Influence of Supervised Disease Understanding and Diabetes Self-Management on Adherence to Oral Glucose-Lowering Treatment in Patients with Type 2 Diabetes. Diabetes therapy 10(4): 1407-1422

[44] Edelman D, Dolor RJ, Coffman CJ et al. (2015) Nurse-led behavioral management of diabetes and hypertension in community practices: a randomized trial. J Gen Intern Med 30(5): 626-633

[45] Egede L E, Williams JS, Voronca DC, Gebregziabher M, Lynch C. (2017) Telephone-Delivered Behavioral Skills Intervention for African American Adults with Type 2 Diabetes: A Randomized Controlled Trial. J Gen Intern Med 32(7): 775-782

[46] Estey A L, Tan MH, Mann K. (1990) Follow-up intervention: its effect on compliance behavior to a diabetes regimen. Diabetes Educ 16(4): 291-295

[47] Kim H S and J A Oh. (2003) Adherence to diabetes control recommendations: impact of nurse telephone calls. J Adv Nurs 44(3): 256-261

[48] Kim H S, J A Oh and Lee H. (2005) Effects of nurse-coordinated intervention on patients with type 2 diabetes in Korea. J Nurs Care Qual 20(2): 154-160

[49] Lange I, Campos S, Urrutia M et al. (2010) [Effect of a tele-care model on self-management and metabolic control among patients with type 2 diabetes in primary care centers in Santiago, Chile]. Rev Med Chil 138(6): 729-737

[50] Lauffenburger J C, Ghazinouri R, Jan S et al. (2019) Impact of a novel pharmacist-delivered behavioral intervention for patients with poorly-controlled diabetes: The ENhancing outcomes through Goal Assessment and Generating Engagement in Diabetes Mellitus (ENGAGE-DM) pragmatic randomized trial. PLos One 14(4): e0214754

[51] Mons U, Raum E, Kramer H et al. (2013) Effectiveness of a supportive telephone counseling intervention in type 2 diabetes patients: randomized controlled study. PLoS One 8(10): e77954

[52] Naik A D, Hundt NE et al. (2019) Effect of Telephone-Delivered Collaborative Goal Setting and Behavioral Activation vs Enhanced Usual Care for Depression Among Adults With Uncontrolled Diabetes: A Randomized Clinical Trial. JAMA Network Open 2(8): e198634-e198634

[53] Nesari M, Zakerimoghadam M, Rajab A, Bassampour S, Faghihzadeh S. (2010) Effect of telephone follow-up on adherence to a diabetes therapeutic regimen. Jpn J Nurs Sci 7(2): 121-128

[54] Oh J A, Kim HS, Yoon K, Choi El. (2003) A telephone-delivered intervention to improve glycemic control in type 2 diabetic patients. Yonsei Med J 44(1): 1-8

[55] O'Connor PJ, Schmittdiel JA, Pathak RD et al. (2015). Randomized trial of telephone outreach to improve medication adherence and metabolic control in adults with diabetes. Diabetes care 2014;37: 3317-3324

[56] Safford M M, Andreae S, *Cherrington* A et al. (2015) Peer Coaches to Improve Diabetes Outcomes in Rural Alabama: a Cluster Randomized Trial. Annals of family medicine 13 Suppl 1: S18-26

[57] Sarayani A, Mashayekhi M, Nosrati M et al. (2018) Efficacy of a telephone-based intervention among patients with type-2 diabetes; a randomized controlled trial in pharmacy practice. JAMA Netw Open 40(2): 345-353

[58] Varney J E, Weiland TJ, Inder WJ and Jelinek GA. (2014) Effect of hospital-based telephone coaching on glycaemic control and adherence to management guidelines in type 2 diabetes, a randomised controlled trial. Intern Med J 44(9): 890-897

[59] Walker E A, Shmukler C, Ullman R, Blanco E et al. (2011) Results of a successful telephonic intervention to improve diabetes control in urban adults: a randomized trial. Diabetes Care 34(1): 2-7

[60] Weinberger M, Kirkman M, Samsa G et al. (1995) A nurse-coordinated intervention for primary care patients with non-insulin-dependent diabetes mellitus: impact on glycemic control and health-related quality of life. J Gen Intern Med 10(2): 59-66

[61] Wolever R Q, Dreusicke M, Fikkan J et al. (2010) Integrative health coaching for patients with type 2 diabetes: a randomized clinical trial. Diabetes Educ 36(4): 629-639

Supplementary 1. Detailed Search terms for Pubmed

1 "diabetes mellitus"[MeSH Terms] OR diabetes mellitus [Text Word]

2 RANDOMIZED CONTROLLED TRIAL

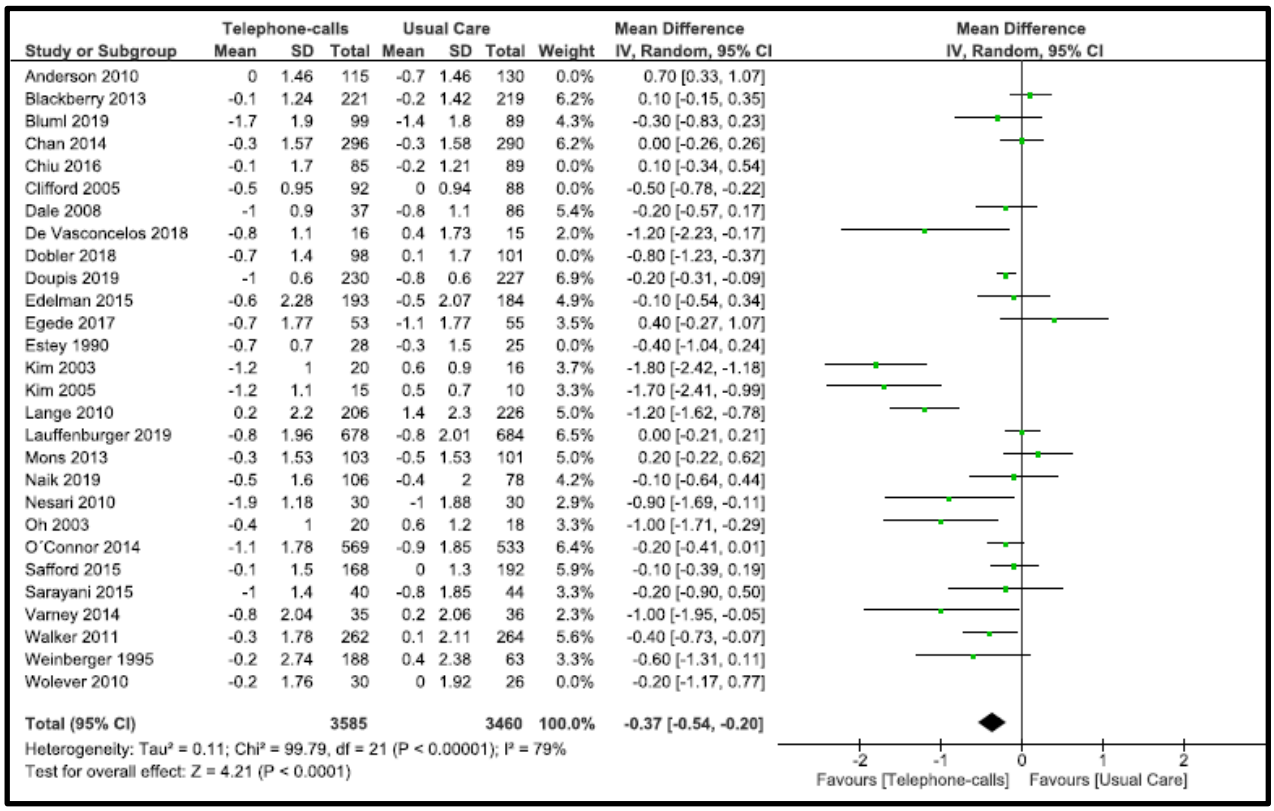
Filter Reference:

McMaster University (2016) Electronic publication: Search filters for MEDLINE in Ovid Syntax and Pubmed translation. Available <https://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx >. Last access November 3rd, 2020

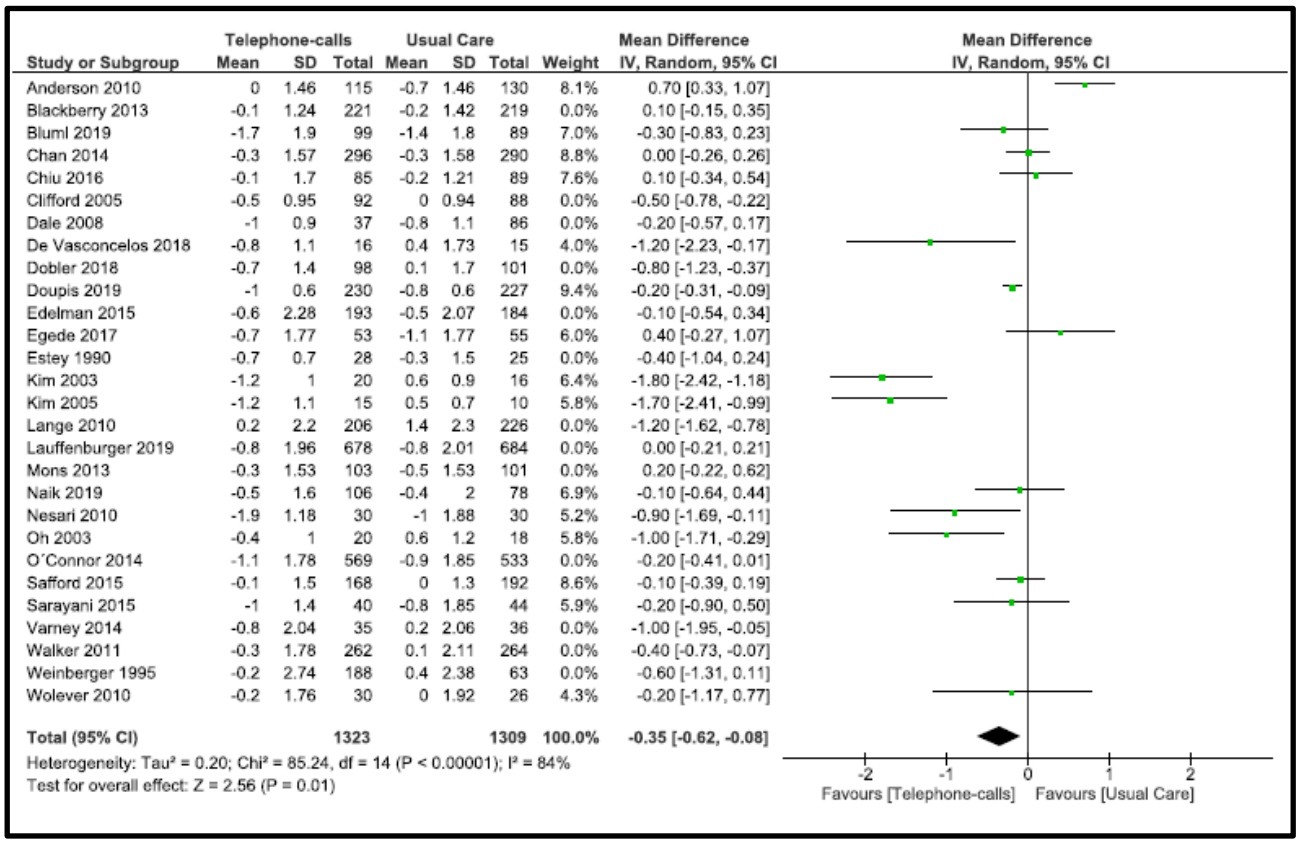
3 "telephone"[MeSH Terms] OR telephone[Text Word]

4 “telemonitoring” [Text Word]

1 AND #2 AND #3 OR #4



Supplementary Fig 1: Forest plot (subgroup analysis) - studies that presented Hba1c > 8% at baseline



Supplementary Fig 2: Forest plot (subgroup analysis) – studies with more intensive intervention (at least biweekly phone-calls)

```
Mixed-Effects Model (k = 17; tau^2 estimator: DL)
tau^2 (estimated amount of residual heterogeneity):     0.1995 (SE = 0.1420)
tau (square root of estimated tau^2 value):             0.4466
I^2 (residual heterogeneity / unaccounted variability): 83.88%
H^2 (unaccounted variability / sampling variability):   6.21
R^2 (amount of heterogeneity accounted for):            0.00%
Test for Residual Heterogeneity:
QE(df = 15) = 93.0798, p-val < .0001
Test of Moderators (coefficient 2):
QM(df = 1) = 0.7720, p-val = 0.3796
Model Results:
            estimate      se     zval    pval    ci.lb   ci.ub
intrcpt      -0.1741  0.4386  -0.3968  0.6915  -1.0338  0.6857
DM duration-0.0386  0.0439  -0.8786  0.3796  -0.1246  0.0475
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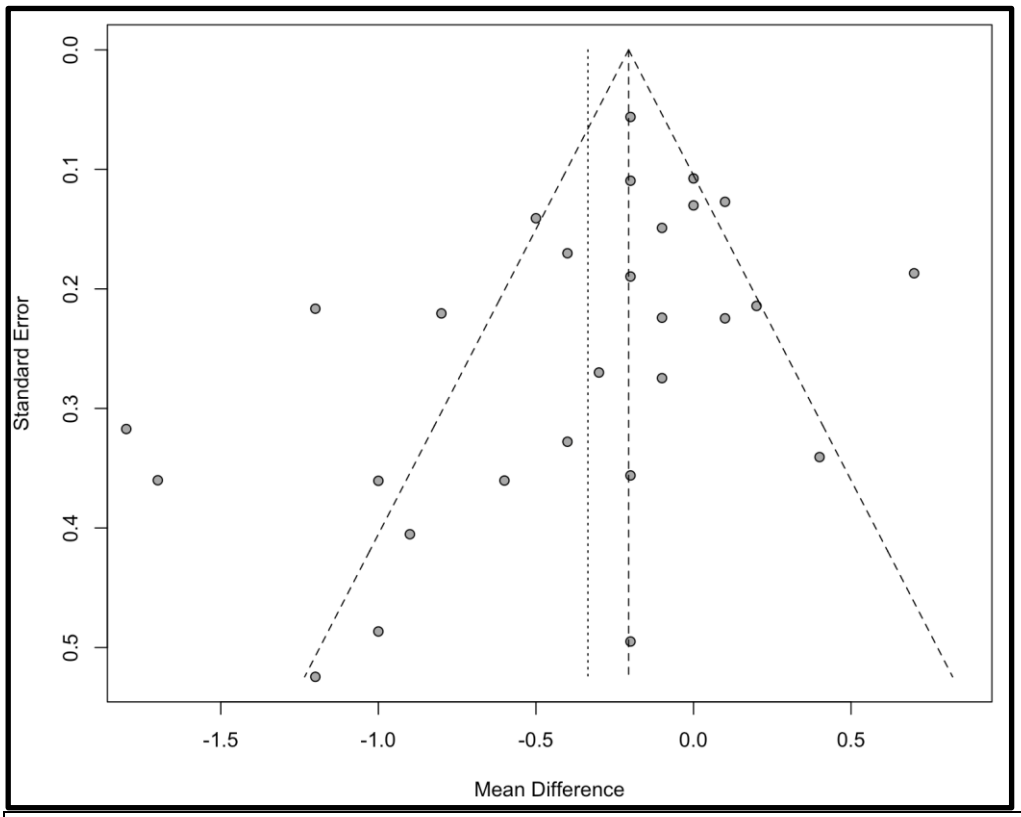
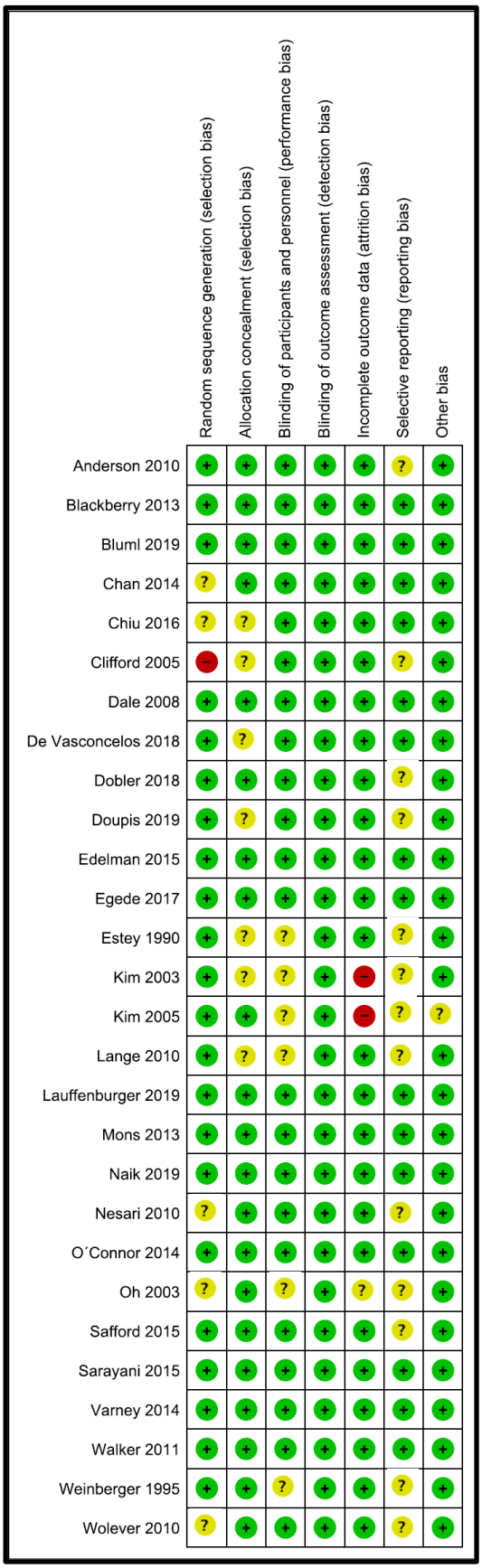
Supplementary Fig 3: Meta-regression correlating T2DM duration and HbA1c



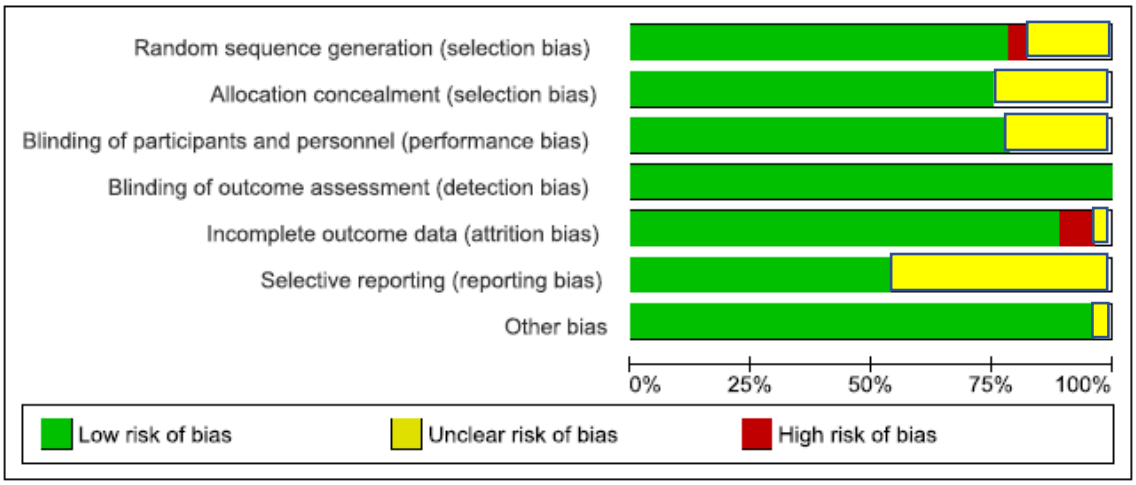
Egger's test			
Intercept	95% Confidence Interval	t	p
-1.418	-3.378-0.542	-1.883	0.0709

Supplementary Fig 4: Funnel-plot for HbA1c and Egger´s test

Supplementary Fig 5: Risk of bias for individual studies

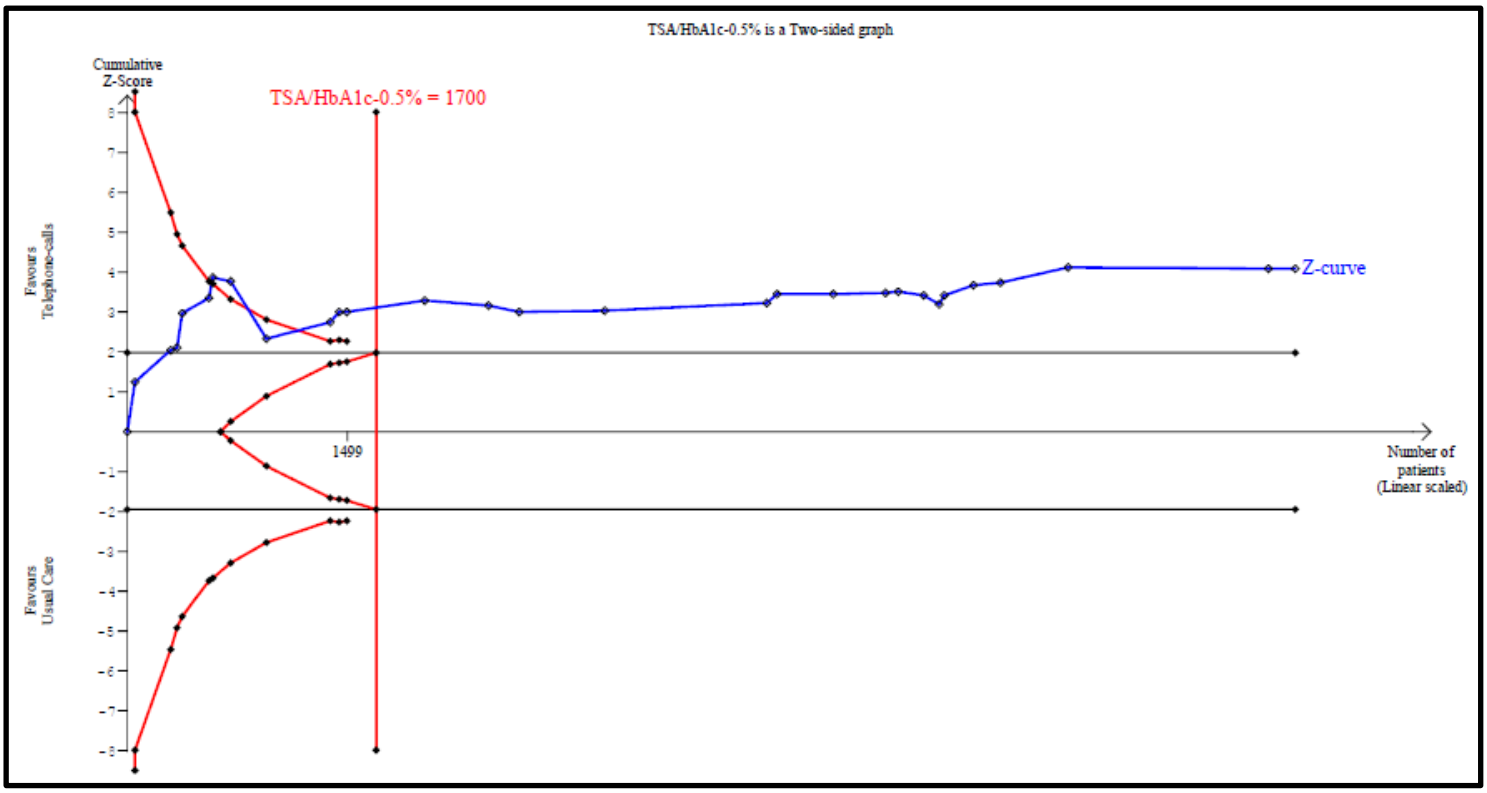


Supplementary Fig 6: Risk of Bias graphic for individual studies



Supplementary Fig 7: TSA analysis for HbA1c outcome

The dashed blue line represents the Z line (cumulative effect size), the continuous red lines represent the harm, benefit, and futility boundaries, and the estimated optimal sample size adjusted to sample size and repeated analysis. The black dashed lines represent the conventional 95% Cis



Supplementary Fig 8. GRADE Assessment

Certainty assessment							Patients		Effect		Certainty	Importance
Number of studies	Study Design	Risk of Bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Telephone-Calls	Usual Care	Relative (95% CI)	Absolut (95% CI)		
28	RCT	Not severe	Severe	Not severe	Not severe	None	4033	3919	-	(-0.5 to -0.17)	⊕⊕⊕◯ MODERATE	Important

CI: Confidence interval; **MD:** Mean difference

Capítulo 2

Effects of Nurse Telesupport Through Telephone Calls on Transition between Specialized and Primary Care in Type 2 Diabetes Mellitus Patients: a Randomized Clinical Trial.

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ABSTRACT

Background: Telemedicine has been increasingly recognized as a tool to improve type 2 diabetes mellitus (T2DM) management, but its role on transition to primary care has not been established yet. In this paper, we present a randomized clinical trial (RCT) aimed to evaluate the effect of a nurse-based telesupport focused on education in well-controlled T2DM patients discharged from a tertiary clinic.

Methods: We designed a CONSORT-compliant 12-month RCT including T2DM patients recruited from a tertiary clinic in south Brazil, with a glycated hemoglobin (HbA1c) <8%, discharged to primary care follow-up and randomized (1:1) to intervention or control groups. Patients were excluded if they have advanced diabetes chronic complications. Intervention group received periodically nurse phone-calls (3,6,9,12 months) focusing on T2DM education and a toll-free number to call the study team with any request about diabetes. Control group received only primary care support. The main outcome was glycemic control (HbA1c) at 12 months. Secondary outcomes were blood pressure, lipid profile, hypoglycemia rate, T2DM chronic complications status and mortality after 12 months.

Results: 147 patients underwent randomization (73 in intervention vs 74 patients in control group) with no differences in baseline data. After one year, we found no differences between study groups in HbA1c (7.46% ±1.37 in intervention vs 7.54% ±1.6 in control group; P= 0.76). HbA1c had a similar small increase from baseline in both groups (0.46% in intervention vs 0.64% in control group) at 12 months, without differences between them (P=0.69). The rate of patients that achieved the glycemic goal remained stable after hospital discharge, without differences between the groups (39% vs 40%, P = 0.90). Secondary outcomes were similar at final evaluation.

Conclusions: A telemedicine intervention based on quarterly nurse phone-calls plus primary care has a similar effect on glycemic control as did exclusive primary care follow-up on T2DM

patients after tertiary clinic discharge. Patients remained with a reasonable glycemic control along the trial period, suggesting that the transition to primary care is safe and possible in terms of glycemic control.

Trial registration: Clinical Trials, NCT02768480. Registered on 29 April 2016.

INTRODUCTION

According to the International Diabetes Federation (IDF), in 2019 diabetes mellitus (DM) prevalence reached 463 million people. Of these, T2DM is responsible for almost 90% [1]. Following the statistics, it is expected that in 2045 this number will have increased in 48%, reaching almost 700 million of people. Brazil occupies the fifth place in the global prevalence ranking, with almost 16 million patients with diabetes, reaching an annual expenditure of almost 1500 dollars/person/year [1].

DM burden seems to be higher in low and middle-income countries due to their elevated prevalence (almost 4 out of 5 diabetic patients live there) and their paucity of resources [1]. There is a relationship between socioeconomic status and glycemic control [2] and the estimated frequency of T2DM patients on glycemic targets in developing countries is disappointing [3]. Thus, creating strategies to optimize resources and help healthcare systems is fundamental to improve T2DM management.

It has been increasingly recognized that primary care plays an important role in diabetes prevention and management. According to the Global Diabetes Plan (2011-2021), primary care workers should deliver essential services for appropriate diabetes care, which includes diagnosis, treatment, monitoring, complications screening and T2DM education [4]. Thus, building a strong primary care can improve health services use. However, an undesirable healthcare network fragmentation, besides an overcrowding of specialized clinics due to the incapacity of meeting the growing care demand have been progressively observed [5].

T2DM patients referred from primary care remain long periods in specialized practices, compromising health system effectiveness [6,7]. In 2019, in a systematic review of 13 observational studies, Hashim et al. demonstrated that specialists provided primary care in almost 2.6% to 65% of their visits. This is due to an inadequate triage and excessive referrals, causing a tertiary care overload, and resulting in longer waiting times for appointments for those

patients who really need specialized care [8]. To improve the health service flow and raise patient's accessibility, strategies for reducing specialized clinics overcrowding are necessary. Discharging T2DM patients from tertiary care to be managed in primary care is a promising alternative. However, currently, this transition of care faces some difficulties. Some barriers pointed by primary care physicians (PCP) are insufficient time to address diabetes needs, knowledge gaps and patient's lack of confidence in primary care team [9]. In the patient´s view, unclearness in rationale of discharge, lack of a discharge plan and concerns about diabetes PCP knowledge are pointed as transition of care issues [10]. Thus, the development of tools that support patient self-management can facilitate this process.

Telemedicine has emerged as an auxiliary in many healthcare scenarios [11]. This term is defined as the use of medical information exchanged from one place to another via electronic communication (fax, short message system, internet, telephone, mobile phone or its applications) to improve patient clinical health status [12]. There is growing evidence of its benefits in T2DM, with a tendency of improvement in glycemic control [13-17]. Regarding its specific use in primary care, it has also been observed a positive effect trend in HbA1c control [18,19]. In 2017, through a meta-analysis, So et al. reviewed the impact of telemedicine interventions in T2DM patient´s glycemic control at primary care settings. They found a significant HbA1c decrease favoring telemedicine strategies when compared to usual care [-0.64%; CI 95% -1.01 to -0.26; $I^2$89%] [19].

In Brazil, in order to support primary care attention, a telemedicine platform was developed in 2013. TelessaudeRS is a service with qualified specialists in different health areas with focus in teleconsultation and tele-education. This service also offers a sort of materials and lectures via website to improve the primary care team knowledge [20]. Furthermore, this program optimizes referrals to specialized care, improving the health system network through an adequate triage, and decreasing waiting lists to specialized clinics [21].

Beyond these remarkable gains, the role of telemedicine as an auxiliary in T2DM transition of care has not been explored yet. Therefore, it remains to be established whether this strategy could be useful to improve the safety of discharging patients to primary care, reducing tertiary care overcrowding and optimizing patient accessibility to diabetes care.

Thus, we conducted a randomized clinical trial aimed to evaluate the efficacy of nurses' periodic telephone-calls focused on education in glycemic control of T2DM patients discharged from a diabetes clinic to primary care.

METHODS

Trial design and oversight

This study was an open label randomized clinical trial aimed to evaluate the effect of nurse telesupport in T2DM patients' glycemic control after being discharged from a specialized university-based endocrinology clinic.

This trial was carried on at Endocrinology Division of Hospital de Clínicas de Porto Alegre, an academic unit of a federal university - Universidade Federal do Rio Grande do Sul (UFRGS) - based in south Brazil. All procedures were approved by the institutional ethics committee and conducted according to the Declaration of Helsinki.

Study procedures were previously published in detail [22] and registered in Clinical Trials database with number NCT02768480. This report follows CONSORT 2010 statement guidelines [23].

Study patients

Inclusion and exclusion criteria

Patients were eligible if they had been diagnosed with T2DM and been discharged from endocrinology ambulatory to primary care with HbA1c <8% (HPLC certified method). The ambulatory discharge decision was discussed with an independent senior specialized staff. Those with severe diabetic kidney disease [glomerular filtration ratio (GFR) <30 mL/min/1.73 m^2], severe peripheral or autonomic neuropathy or symptomatic ischemic heart disease were excluded. All selected patients provided a written informed consent before study entry.

Study procedures

All eligible patients, after agreement with the written informed consent, underwent randomization. The randomization sequence was generated online, with a 1:1 ratio, using random blocks of four and six patients. The researcher involved in the randomization process was not involved in the recruitment. Patients were allocated sequentially through dark-brown sealed envelopes that were opened only after provided consent. No stratification method was used. The study was not blinded to participants, trial research team and outcome assessors. Statistical analysis was performed in blinded fashion.

At the time of ambulatory discharge, both groups received printed educational material with information about diet, foot care and insulin application. They also received an official discharge document addressed to their primary care physician with individualized information about individual glycemic targets, diabetes treatment, current diabetes complications and hypoglycemic risk. A TelessaudeRS toll-free number was mentioned in this document to help the primary care team in case management if necessary. All patients were guided to seek their primary care clinic to schedule the routine follow-up.

Besides the primary care treatment, the intervention group received periodic nurse phone calls (3, 6, 9, 12 months after discharge). Trained nurses discussed relevant topics and provided diabetes education. They reviewed therapy adherence, techniques of insulin application, foot care, treatment side effects, frequency of physician visits and oriented hypoglycemia management. Moreover, this group was able to call a free phone number and ask a specialized team about their medical treatment, diet, or any occasional doubt. Due to local legal determinations, changes on medication were not allowed. In case of need, the research team recommended a visit to the primary care physician for pharmacological treatment adjustments.

The control group was followed by primary care exclusively, with routine visits established by the public health system. They also received periodic phone calls (3, 6, 9, 12 months after discharge) just for follow-up and personal data update, but without any intervention.

After 12 months, both groups underwent in-person visits with a trained research team. At this time, this team reviewed diabetes symptoms, prescribed treatment, hypoglycemia episodes, emergency visits and chronic complications status. Groups were also submitted to a physical and laboratory evaluation.

Data collection methods

At baseline, demographic and health data were collected through a standardized questionnaire. Information about glycemic control (HbA1c, fasting plasma glucose), renal function (estimated GFR and albuminuria), lipid profile (total cholesterol, HDL-cholesterol, and triglycerides) and treatment prescribed were obtained through medical records. Follow-up information was collected quarterly through a questionnaire by telephone to verify patient's participation and minimize dropouts.

At final assessment, an interview was performed with a questionnaire completion. This standardized questionnaire assessed: demographic information; cardiovascular and morbid history; smoking status; statin and antiplatelet use; and diabetes treatment. Besides that, patients were asked about hypoglycemia episodes rate, diabetes decompensations resulting in emergency visits and tertiary care referrals rate. To obtain cardiovascular events occurrences, we used Rose questionnaire and self-reported events. A physical exam with evaluation of blood pressure (after 5 minutes of seated rest), body weight and height was performed. GFR was calculated through CKD-EPI equation [24]. HbA1c, fasting plasma glucose, creatinine, lipids profile and albuminuria were evaluated at this moment.

Outcomes

The 12-month primary outcome was glycemic control measured by HbA1c (ion-exchange HPLC certified method). As secondary outcomes, we defined being on HbA1c glycemic target, achieving a HbA1c less than 8%, systolic and diastolic blood pressure levels, use of statin and antiplatelet therapy, hypoglycemic episodes rate, lipid profile, development or worsening of nephropathy, referrals to tertiary service, emergency visits, cardiovascular events (ischemic heart disease, stroke, peripheral vascular disease and carotid stenosis) and mortality.

Statistical analysis

A sample of 63 patients in each treatment arm was calculated to reach a between-group difference of 1% in HbA1c after one year. We considered a standard deviation of 2%, an alpha of 0.05 and a statistical power of 80%. Considering a missing rate of 10%, we recruited 147 patients.

Variables with normal distribution were expressed as mean ± standard deviation, and asymmetric variables as median (interquartile range). Categorical variables were presented as absolute counts and percentages and compared by chi-square test. Student's t-test was used

to compare normal continuous variables and Mann-Whitney to compare non-parametric ones. Main outcomes were presented through intention-to-treat (all included patients) and per-protocol (received at least one phone call) analysis. To analyze differences in outcomes between and within paired groups along study period, we used the GEE (generalized estimating equation) statistical model for continuous variables and McNemar for categorical ones. To estimate possible predictive factors associated with main outcomes, we used the robust Poisson regression analysis. All analyses were performed with the use of SPSS software, version 24.

RESULTS

Study patients

From July 2015 to June 2017, a total of 1253 patients were screened for trial participation. After applying the eligibility criteria, 147 participants underwent randomization (73 patients on intervention and 74 on control group - Figure 1).

Baseline characteristics were similar between the two groups (Table 1). Participants mean age was 64 years, 61.9% were women and body mass index (BMI) was 32±6 kg/m² at first assessment. The mean baseline HbA1c value was 6.99±0.69% and 45.6% of them were on diabetes established target. Estimated GFR was 77±21 mL/min/1.73 m² and median albuminuria was 7.2 (3 - 34.7) mg/L. Regarding treatment, 53.7% of the total sample used insulin and 91.2% used oral antidiabetic drugs.

The trial finished in July 2018, after completing the last final planned visit. As established a priori, the mean follow-up was 12 months. During this period, 8 patients discontinued the study, with a trial adherence rate of 94.5%. The clinical characteristics of these patients were similar to the remaining patients. Among the follow-up losses, 6 patients withdrew consent (Figure 1). No patient died along the trial period.

Effect on glycemic control

HbA1c was not different between the two groups after one-year of follow-up: 7.46 ±1.37% in the intervention group vs 7.54±1.6% in control group; P=0.76. Along the trial period, we found a worsening in glycemic control in both groups. HbA1c significantly increased from 7.0± 0.67% at baseline to 7.46± 1.37% at 12 months (P=0.0) in intervention group, and from 6.9± 0.7% to 7.54±1.6% in control group (P = 0.002), without differences between them (P= 0.69 – Table 2; Figure 2). Despite the increase in HbA1c, we found no differences between two groups in the rate of patients at HbA1c target along the trial period (P=0.905) (Table 2). In intervention group, the frequency of patients at glycemic target varied from 44% at baseline to 39% at 12-months (P=0.373), and in control group this rate varied from 48% at baseline to 40% at final assessment (P=0.233) (Table 2; Figure 3). When we assessed the possible predictors of reaching diabetes glycemic goal after 12 months, we found no effect of BMI, age, gender, study group or education-years (Supp. Table 1). Stratifying patients according to the HbA1c final level, we found that most of them reached a HbA1c value less than 8% (the value established as the criteria for hospital discharge) - 74.3% in intervention vs 84.2% in control group (P= 0.2) , remaining with a reasonable glycemic control in the end of study period. There were also no differences in hypoglycemia episodes incidence during the month before study completion (RR 1.1; CI 95% 0.71 to 1.71).

Effect on secondary outcomes

Regarding blood pressure, we found no differences between the two groups after 12 months and along the study period (Table 2). At final assessment, systolic blood pressure was 135±19 mmHg in intervention group vs 132 ±19 mmHg in control group; P=0.31. Diastolic blood pressure also reached similar values in two study groups (77±12 mmHg in intervention vs 77±12

mmHg in control group; P=0.77, Table 2), representing a fairly good control. BMI was also similar in the final evaluation: 31.3 ±6 kg/m² in intervention group vs 31.4 ±6 kg/m² in control group; p=0.96, and without changes along trial period (Table 2).

At final assessment, there were also no differences in total cholesterol (163 ±43 mg/dL vs. 164±40 mg/dL in intervention and control group, respectively; p=0.84), HDL–cholesterol (48±16 mg/dL vs 48±14 mg/dL in intervention group and control group, respectively; p= 0.57) and triglycerides [130 (102-182) mg/dL vs 147 (104-209) mg/dL in intervention group and control group, respectively; p=0.52].

Analyzing renal outcomes, we found a worsening in albuminuria after 12 months in both study groups (Table 2). In the intervention group, albuminuria significantly increased from 6.5 (3-31) mg/L at baseline to 18 (4.5-69) mg/L at final evaluation (P=0.0). The same pattern was found in the control group [8.7 (3-35) mg/L at baseline to 19.8 (5-60.3) mg/L in 12-months; P=0.001], but without differences between two groups along study period (P= 0.51) (Table 2). Evaluating the progression through albuminuria categories (normal, microalbuminuria and macroalbuminuria) along 12 months, we found no differences between groups (30% of intervention patients progressed vs 21% in control group; P=0.239). GFR did not change significantly along study-time. Intervention group had a baseline GFR of 76±22 mL/min/1.73 m² and a final value of 80±25 mL/min/1.73 m² (P=0.29). Similarly, the control group GFR changed from 77±20 mL/min/1.73 m² at baseline to 75±21 mL/min/1.73 m² after one year (P=0.16) (Table 2). The number of patients that developed reduced GFR (<60 mL/min/1.73 m²) were similar between intervention and control groups, respectively, 4.3% and 8.7%; P = 0.31. Regarding diabetes kidney disease (DKD) progression measured by change in KDIGO stages during the study period, there were no differences between groups (11% of intervention patients progressed DKD vs 20% in control group; P=0.163), and we did not find an association between

DKD progression and baseline albuminuria or frequency of patients on glycemic target (Suppl table 1).

The analysis of cardiovascular composite events (ischemic heart disease, stroke, and peripheral vascular disease) showed no difference between groups (22% of cardiovascular events incidence in intervention and 37% in control group; P= 0.057). When outcomes were analyzed individually, we found a significant difference favoring control group in stroke incidence (Fig. 4).

Regarding the referral rate to tertiary care, 6% of intervention participants and 10% of the control group were referred to diabetes clinics; P= 0.34. During the study period, both groups also had a similar rate of emergency visits for T2DM reasons (0.21 visits/person in intervention vs 0.29 visits/person in control group; P= 0.5).

DISCUSSION

Our study is the first trial aimed to evaluate the telemedicine effect on T2DM patients discharged from a diabetes clinic to primary care. Among both groups, HbA1c slightly increased from baseline with a similar pattern between telephone-calls plus usual care and usual care alone, ensuring the safety and efficacy of discharge from tertiary to primary care in well-selected cases.

The HbA1c increase in the intervention group reached 0.4% after one year. This variation seems to be irrelevant both in the clinical and laboratory aspects. Going back to classics, the UKPDS group showed that a HbA1c variation of 0.6% was necessary to produce clinical benefit regarding diabetes related endpoints [25,26]. Furthermore, according to National Glycohemoglobin Standardization Program (NGSP) concept [27], developed on DCCT period [28], when we analyze the HbA1c method, we must assume that an inter-assay imprecision and a biological variation exists [29]. It is estimated that the HbA1c method can achieve a biological

coefficient variation of 6.8% [30,31]. Added to the analytical variation it can reach a variation of 10-20% [30]. Thus, a meaningful reference change value in HbA1c would be of at least 0.75% above the baseline of 7.5%. Moreover, despite the numerical increase in HbA1c, both groups remained in the glycemic target after one year of discharge. From this data, we can conclude that discharging T2DM patients with a reasonable glycemic control and without severe complications is safe and it is not associated with DM decompensation in this time frame (12 months). These findings can draw attention to an adequate T2DM management by primary care professionals and might help to improve the network system due to an incentive to ambulatory discharge and a reduction in tertiary care overcrowd.

Our findings are in accordance with other published studies [32-37]. In 2010, Anderson et al. studied the effect of nurse phone-calls on uncontrolled T2DM patients during a 12-month RCT and showed no differences on glycemic control compared to usual care [32]. More recently, in 2017, Egede et al. did not find a benefit on T2DM patients' HbA1c in a one-year trial comparing motivational phone calls with usual care [33]. In 2019, Bluml et al. also tested the role of telephone support focused on T2DM education as an auxiliary to usual care through a RCT and found no differences in HbA1c [34]. However, other studies have already shown a benefit of phone-calls intervention in T2DM glycemic control [38-40]. In 2005, Clifford et al. showed an improvement in HbA1c (-0.5%) after one-year follow-up in patients who received periodic education phone-calls by pharmacists [38]. In 2018, Dobler et al. showed a decrement in HbA1c of 0.7% in patients that received monthly phone-calls by nurses [39].

As strengths, we did a well-designed clinical trial with a small percentage of follow-up losses (adherence rate of 94.5%), empowering the results shown above. Furthermore, our patients were not in artificially favorable conditions. Our results were necessarily influenced by health care system problems and patients' context, turning our trial into real-world evidence. This research also had some limitations. First, we included T2DM patients with HbA1c less than

8%, which generate a sample with a reasonable glycemic control, turning difficult to achieve greater beneficial differences on HbA1c after one year. In 2011, Chamany et al. evaluated the effect of phone calls education intervention in low income T2DM patients through a RCT. They found a significant difference in HbA1c of 0.4% favoring intervention (95% CI 0.09-0.74; p = 0.01), with a better effect when baseline HbA1c was greater than 9% [41]. However, we were able to demonstrate that the patients could keep a fairly good glycemic control. We also cannot generalize our results to patients with uncontrolled T2DM or severe complications, highlighting the importance of properly selecting patients for primary care referral. Second, previous studies evaluated phone-call interventions with changes on diabetes treatment (oral antidiabetics and insulin titration) and showed more expressive effects on glycemic control [42-44]. However, according to Brazilian law, nurses are not allowed to do any changes on patient medication, so our intervention was limited to education advice, which might have compromised our results. Third, the control group also received phone-calls, but without any intervention, just for follow-up. This might have enhanced usual care evaluation and underestimated intervention effect.

In conclusion, our randomized clinical trial showed that telemedicine intervention through quarterly nurse education phone calls had no effect on glycemic control when compared to usual care on T2DM patients after one year of tertiary care discharge. Despite this, both intervention and control groups remained on the diabetes individual target at this period, showing that discharge patients from tertiary care to primary care is safe, an important finding in terms of public healthcare.

Declarations

Ethical approval and consent to participate

This study was evaluated and approved by the Institutional Review Board, Hospital de Clínicas de Porto Alegre (IRB: 150503). A trained research interviewer obtained written informed consent before randomization and after explaining the research procedures.

Consent to publish: Not applicable

Availability of data and materials

Research files will be kept by the investigators in binders stored at the research office. Study data will be handled unidentified. Only the researchers responsible for analyses will have access to the final dataset; the sponsor will not have access to data. Following the main publication of this trial, we plan to provide the unidentified dataset to interested personnel by contacting the authors and informing them of the planned analyses, which will be evaluated by the lead investigator of the study.

The International Committee of Medical Journal Editors authorship criteria and the CONSORT Statement was followed.

Competing Interests

The authors declare no competing interests.

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Authors Contributions

AMSM: study design, data collection and analysis, manuscript writing, and final approval of the manuscript. DVR: study design, data collection and analysis, manuscript writing, and final approval of the manuscript. CBF: data collection and manuscript writing. SC: data collection. LAF: substantial contributions to implementation of planned intervention. LFS: substantial contributions to implementation of planned intervention. AMM: substantial contributions to implementation of planned intervention. NK: conception and design, critical revision, and final approval of the manuscript. EH: conception and design, financial support, final approval of the manuscript. SPS: conception and design, critical revision, and final approval of the manuscript. All persons listed as authors have contributed to preparing and approved the manuscript and that International Committee of Medical Journal Editors (ICMJE) criteria for authorship have been met.

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References

[1] International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, Belgium: International Diabetes Federation, 2019. Available in: < http://www.diabetesatlas.org> Last access in November 10, 2020

[2] Silva-Tinoco R, Cuatecontzi-Xochitiotzi T, De la Torre-Saldaña V et al. (2020) Role of social and other determinants of health in the effect of a multicomponent integrated care strategy on type 2 diabetes mellitus. International Journal for Equity in Health 19(75):1-11

[3] Farias CB, Coelli S, Satler F, Brondani L, Zelmanovitz T, Silveiro SP. (2020) HbA1c and Blood Pressure Levels in Type 2 Diabetes: How many patients are on target? Canadian Journal of Diabetes DOI: https://doi.org/10.1016/j.jcjd.2020.10.002

[4] International Diabetes Federation. Global Diabetes Plan 2011-2021. (2011) Brussels Belgium: International Diabetes Federation, 2019. Available in: < nhttp://www.diabetesatlas.org> Last access in November 10, 2020

[5] Harzheim E, Gonçalves MR, Umpierre RN et al. (2016) Telehealth in Rio Grande do Sul, Brazil: Bridging the Gaps. Telemedicine and E-Health 22 (11): 1-7

[6] Beaser RS, Okeke E, Neighbours J et al. (2011) Coordinated primary and specialty care for type 2 diabetes mellitus, guidelines, and systems: an educational needs assessment. Endocr Pract 17(6):880-90

[7] Hansen TK, Orskov C, Brockstedt H, Hornum H, Hansen KW. (2014) Patients referred with type 2 diabetes remain in specialist care for a long period. Dan Med J 61(4): A798

[8] Hashim MJ. (2020) Provision of primary care by specialist physicians: a systematic review. Fam Med Com Health 8: e000247

[9] Brez S, Rowan M, Malcolm J et al. (2009) Transition from specialist to primary diabetes care: A qualitative study of perspectives of primary care physicians. BMC Family Practice 10 (39): 1-8

[10] Dutton H, Rowan MS, Liddy C et al. (2014) Patient Perspectives on Discharge from Specialist Type 2 Diabetes Care Back to Primary Care: A Qualitative Study. Can J Diabetes 38(3):191-7

[11] Dorsey ER, Topol EJ. (2020) Digital Medicine – Telemedicine 2020 and the next decade. Lancet 395: 859

[12] Lee, SWH; Ooi, L and Lai YK. (2017) Telemedicine for the Management of Glycemic Control and Clinical Outcomes of Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Studies. Frontiers in Pharmacology 8: 1-8

[13] Tchero H, Kamgambega P, Briatte C, Brunet-Houdard S, Retali GR, Rusch E. (2018) Clinical Effectiveness of Telemedicine in Diabetes Mellitus: A Meta-Analysis of 42 Randomized Controlled Trials. Telemed J E Health 25(7):569-583

[14] Faruque LI, Wiebe N, Ehteshami-Afshar A et al. (2017) Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials. CMAJ 189: E341-64

[15] Lee PA, Greenfield G, Pappas Y. (2018) The impact of telehealth remote patient monitoring on glycemic control in type 2 diabetes: a systematic review and meta-analysis of systematic reviews of randomized controlled trials. BMC Health Services Research 18: 1-10

[16] Greenwood DA, Gee PM, Fatkin KJ, Peeples M. (2017) A Systematic Review of Reviews Evaluating Technology-Enabled Diabetes Self-Management Education and Support. Journal of Diabetes Science and Technology 11(5) 1015–1027

[17] Wu C, Wu Z, Yang L et al. (2018) Evaluation of the clinical outcomes of telehealth for managing diabetes A PRISMA-compliant meta-analysis. Medicine (Baltimore) 97(43):e12962

[18] Heitkemper EM, Mamykina L, Travers J, Smaldone A. (2017) Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. Journal of the American Medical Informatics Association 0(0): 1–13

[19] So CF, Chung JWY. (2017) Telehealth for diabetes self-management in primary healthcare – a systematic review and meta-analysis. Journal of Telemedicine and Telecare 0(0):1-9

[20] Ministério da Saúde/Governo Federal do Brasil. Electronic publication in: Telessaúde – RS, 2020. Available at < http:// www.ufrgs.br/telessauders/>. Last access in april 01 2020.

[21] Pfeil JN, Rados DV, Roman R et al. (2020) A telemedicine strategy to reduce waiting lists and time to specialist care: A retrospective cohort study. Journal of Telemedicine and Telecare0(0): 1–8

[22] Moreira AM et al. Effects of nurse telesupport on transition between specialized and primary care in diabetic patients: study protocol for a randomized controlled trial. Trials, 222: p. 1-6, 2017

[23] Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. (2010) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 340:c869. doi: 10.1136/bmj.c869

[24] Schwandt A et al. (2017) Comparison of MDRD, CKD-EPI, and Cockcroft-Gault Equation in Relation to Measured Glomerular Filtration Rate Among a Large Cohort With Diabetes. J Diabetes Complications 31: 1376-1383

[25] UKPDS group. (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet 352: 855-865

[26] UKPDS group. (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet 352: 837-53

[27] National Glycohemoglobin Standardization Program. Electronic publication in: NGSP, 2010. Available at <http://www.ngsp.org/>. Last access in November 2020

[28] The Diabetes Control and Complications Trial Research Group. (1993) The Effect of Intensive Treatment of Diabetes on The Development and Progression of Long-term Complications in Insulin-dependent Diabetes Mellitus. The New England Journal of Medicine 329: 977-86

[29] Netto AP et al. (2009) Atualização sobre hemoglobina glicada (HbA1C) para avaliação do controle glicêmico e para o diagnóstico do diabetes: aspectos clínicos e laboratoriais. J Bras Patol Med Lab 45 (1): 31-48

[30] McCormack JP and Holmes DT. (2020) Your results may vary: the imprecision of medical Measurements. BMJ 368: 1-5

[31] European Federation of Clinical Chemistry and Laboratory Medicine. Electronic publication in: EFLM, 2018. Available at < https://biologicalvariation.eu/>. Last access in November 2020

[32] Anderson D R, Christison-Lagay J, Villagra V, Liu H Dziura. (2010). Managing the space between visits: a randomized trial of disease management for diabetes in a community health center. J Gen Intern Med 25(10): 1116-1122

[33] Egede L E, Williams JS, Voronca DC, Gebregziabher M, Lynch C. (2017) Telephone-Delivered Behavioral Skills Intervention for African American Adults with Type 2 Diabetes: A Randomized Controlled Trial. J Gen Intern Med 32(7): 775-782

[34] Bluml B M, Kolb LE, Lipman R (2019). Evaluating the impact of year-long, augmented diabetes self-management support. Population health management 22(6): 522-528

[35] Blackberry I D, Furler JS, Best JD et al. (2013) Effectiveness of general practice based, practice nurse led telephone coaching on glycaemic control of type 2 diabetes: the Patient Engagement and Coaching for Health (PEACH) pragmatic cluster randomised controlled trial. BMJ Clinical research 347: f5272

[36] Lauffenburger J C, Ghazinouri R, Jan S et al. (2019) Impact of a novel pharmacist-delivered behavioral intervention for patients with poorly-controlled diabetes: The ENhancing outcomes through Goal Assessment and Generating Engagement in Diabetes Mellitus (ENGAGE-DM) pragmatic randomized trial. PLos One 14(4): e0214754

[37] Sarayani A, Mashayekhi M, Nosrati M et al. (2018) Efficacy of a telephone-based intervention among patients with type-2 diabetes; a randomized controlled trial in pharmacy practice. JAMA Netw Open 40(2): 345-353

[38] Clifford, R M, Davis WA, Batty KT, Davis T. (2005) Effect of a pharmaceutical care program on vascular risk factors in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 28(4): 771-776

[39] Dobler A, Pollmann H, Raspe H, Belnap B, Farin E, Mittag O. (2018) Telephone-delivered lifestyle support with action planning and motivational interviewing techniques to improve rehabilitation outcomes. Rehabilitation psychology 63(2): 170-181

[40] Varney J E, Weiland TJ, Inder WJ and Jelinek GA. (2014) Effect of hospital-based telephone coaching on glycaemic control and adherence to management guidelines in type 2 diabetes, a randomised controlled trial. Intern Med J 44(9): 890-897

[41] Chamany S et al. (2015) Telephone Intervention to Improve Diabetes Control: A Randomized Trial in the New York City A1c Registry. Am J Prev Med 49(6): 832–841

[42] Davidson MB and Davidson SJ. (2019) Effect of Remote Glucose Monitoring Utilizing Computerized Insulin Dose Ajustment Algorithms: A Pilot Project. Diabetes Ther, 10: 523–533

[43] Tang PC et al. (2013) Online disease management of diabetes: Engaging and Motivating Patients Online with Enhanced Resources-Diabetes (EMPOWER-D), a randomized controlled trial. J Am Med Inform Assoc 20: 526–534

[44] Stone RA et al. (2010) Active Care Management Supported by Home Telemonitoring in Veterans with Type 2 Diabetes. Diabetes Care 33: 478–484

Figure 1. Study Flowchart

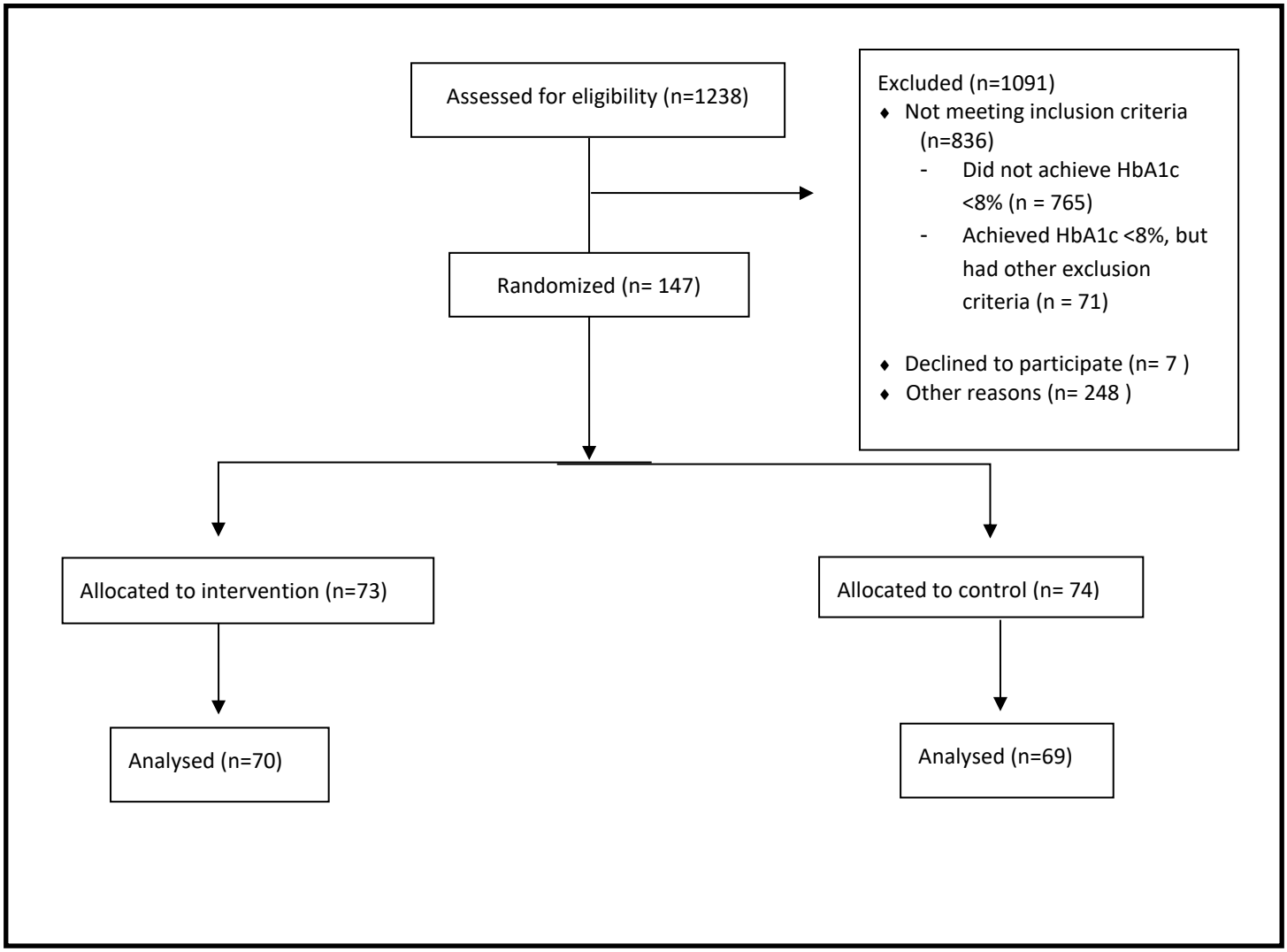


Table 1. Baseline clinical and laboratory characteristics of T2DM patients in intervention and control groups.

Variable	**Intervention** (N=73)	**Control** (N=74)	**P value**
Age (years)	64 ±12	64 ± 10	0.95
Women n (%)	45 (62%)	46 (62%)	0.94
Ethnicity n (%) †	49 (67%)	46(62%)	0.34
(W/B/O)	14 (19%)	9 (12%)	
	9 (13%)	19 (26%)	
Current smoker n (%)	2 (3%)	6 (8%)	0.15
Hypertension n (%)	61(84%)	56 (76%)	0.23
DM duration (years)	16 ± 11	14 ± 9	0.30
Oral antidiabetic n (%)	64 (87%)	70 (95%)	0.13
Insulin use n (%)	41 (52%)	38 (48%)	0.55
Statin therapy n (%)	52 (71%)	56 (76%)	0.54
Antiplatelet therapy n (%)	31 (42%)	33 (45%)	0.79
DKD n (%)	15 (21%)	16 (22%)	0.6
(micro/macroalb)	1 (1%)	3 (4%)	
Cardiovascular disease n (%)	18(25%)	15 (20%)	0.52
Glucose (mg/dl)	134 ± 38	122 ±44	0.08
Cholesterol (mg/dl)	168 ± 42	162 ± 33	0.37
HDL (mg/dl)	45 ± 14	47 ± 18	0.59
Triglycerides (mg/dl)	136 (97.7-193)	127 (92-187)	0.87

Plus–minus values are mean±SD and median (IQR); interquartile range.

†Ethnicity was reported by patients

DKD: diabetes kidney disease; W:White, B:Black, other:O

Table 2. Main outcome differences over 12-month period between intervention and control groups.

Outcomes	Intervention			Control			
	Baseline	**12 months**	**P-value**	**Baseline**	**12 months**	**P-value**	**P-value between groups**
HbA1c (%)	7.0 ± 0.67	7.46 ± 1.37	0.00	6.9 ± 0.7	7.54±1.6	0.002	0.696
Patients on HbA1c target N (%)	32(44%)	27(39%)	0.373	35(48%)	27(40%)	0.233	0.905
SBP (mmHg)	139 ±19	135±19	0.152	136±21	132±19	0.17	0.907
DBP (mmHg)	80±9	77±12	0.102	79±11	77±12	0.258	0.785
BMI (Kg/m^2)	31 ± 6	31±6.3	0.52	31 ± 6	31±6.3	0.207	0.18
GFR (mL/min/1.73m^2)	76± 22	80±25	0.29	77 ± 20	75±21	0.166	0.08
Albuminuria (mg/l)	6.5 (3-31)	18 (4.5-69)	0.00	8.7 (3-35)	19 (5-60)	0.001	0.518

Plus–minus values are means±SD and median (IQR) or number of cases (%). IQR denotes interquartile range

GFR: glomerular filtration rate; BMI: body mass index; HbA1c: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure

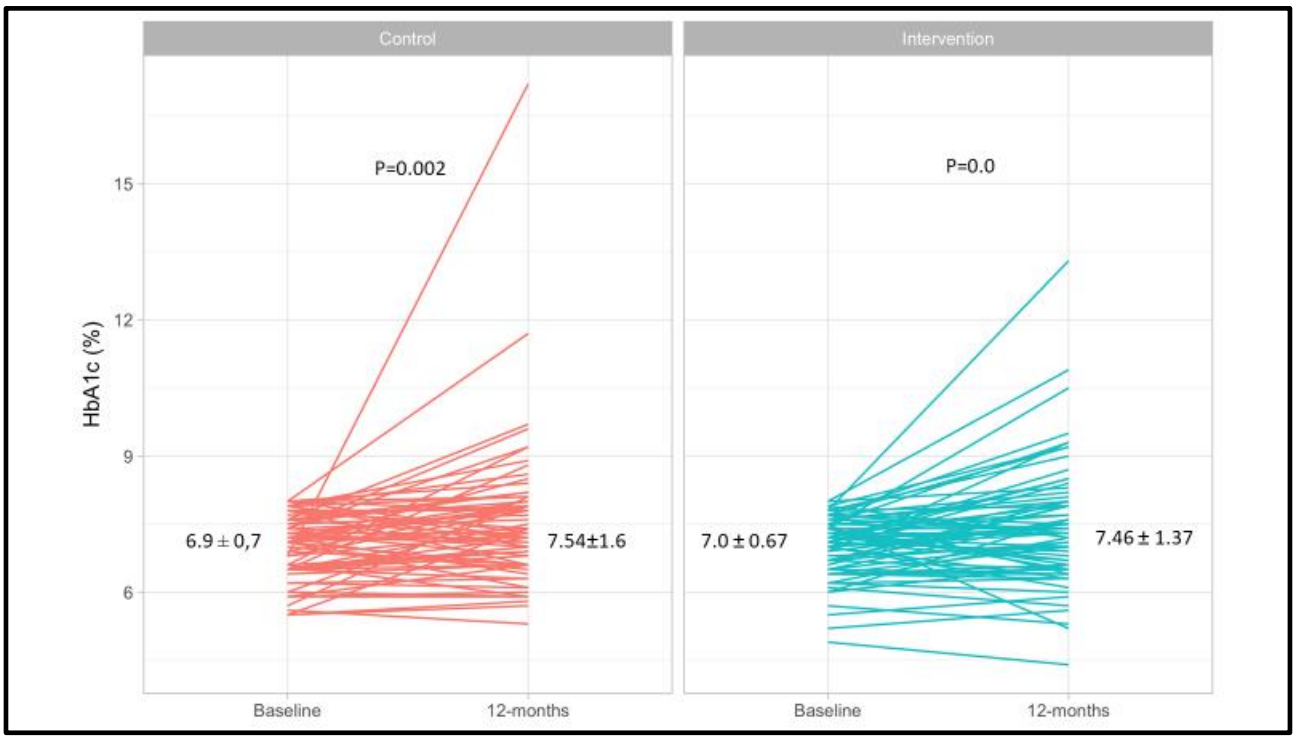


Figure. 2 HbA1c levels over 12 months in intervention and control groups.

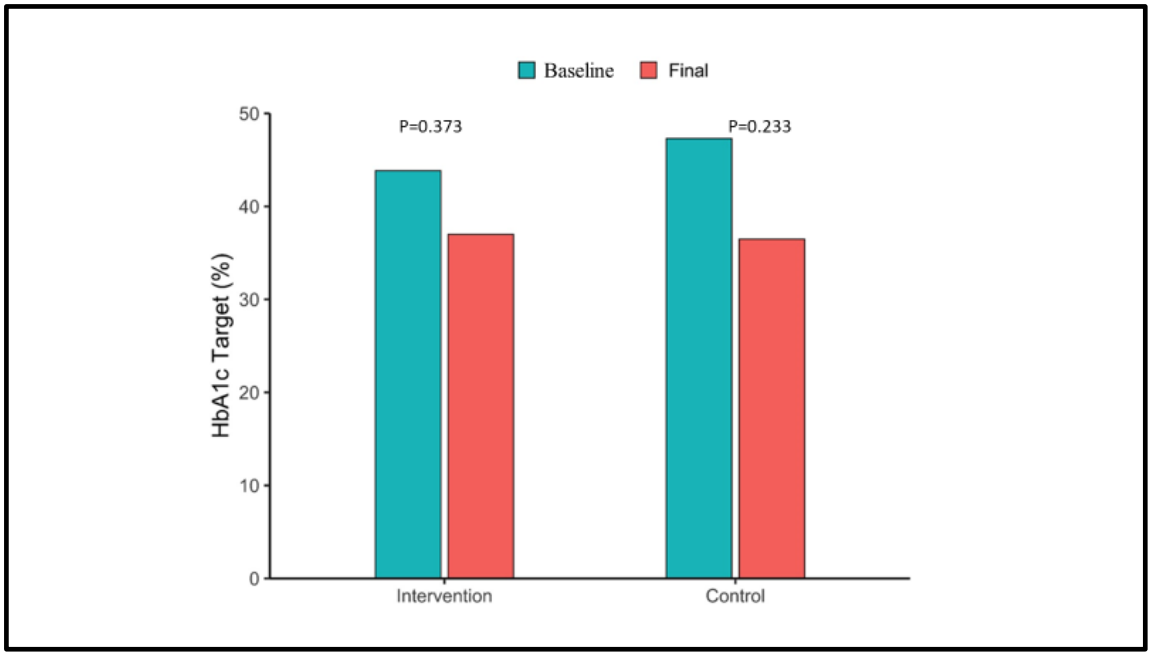
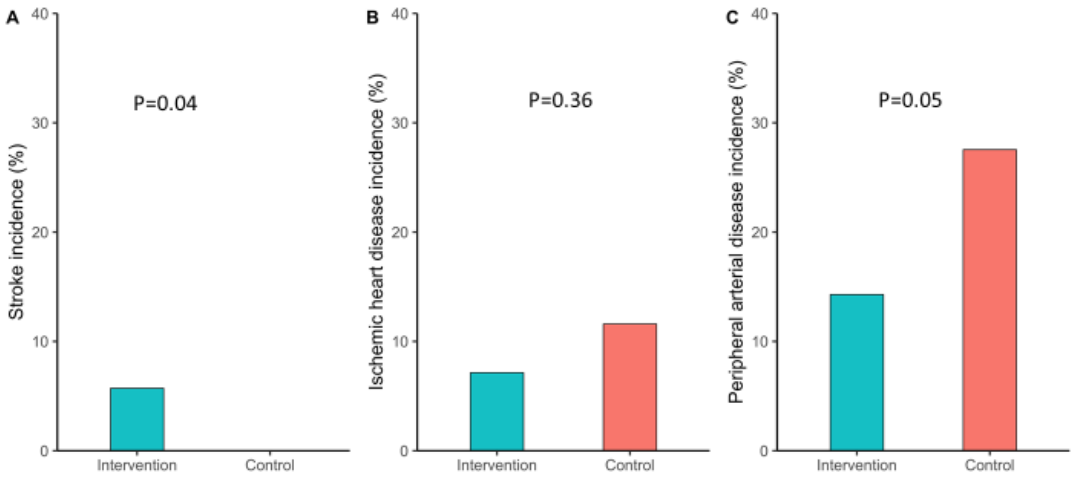


Figure 3. Frequency of patients on glycemic target along 12 months in intervention and control groups.

Figure 4. Incidence of cardiovascular events at 12 months of follow-up in intervention and control groups.



Suppl. Table 1. Predictors of cardiovascular disease incidence, reaching HbA1c target and DKD progression

Predictors	B	Standard Error	Significance	Prevalence ratio	95% CI
			CVD incidence		
Hypertension	0.307	0.418	0.463	1.35	0.59-3.08
Statin use	0.21	0.379	0.58	1.23	0.58-2.59
Allocated group (Intervention)	-0.50	0.319	0.11	0.60	0.32-1.12
			Reaching HbA1c target		
BMI	0.002	0.019	0.938	1.00	0.96-1.04
Age	-0.006	0.010	0.564	0.99	0.97-1.01
Gender (female)	0.115	0.228	0.613	1.12	0.71-1.75
Scholarity (years)	0.011	0.028	0.698	1.01	0.95-1.06
Allocated group (Intervention)	-0.85	0.217	0.698	0.919	0.60-1.40
			DKD progression		
Out of HbA1c target at baseline	0.326	0.656	0.714	1.386	0.3-5.02
Albuminuria	-0.002	0.0018	0.189	0.998	0.994-1.00
Allocated group (Intervention)	-0.394	0.423	0.352	0.674	0.29-1.54

CVD: cardiovascular disease; DKD: diabetic kidney disease

*B denotes beta value; CI 95%: confidence interval 95%

* Data evaluated through Poisson regression

CONSIDERAÇÕES FINAIS

O *Diabetes Mellitus tipo 2* (DM2) é uma condição de alta prevalência e de custo expressivo, especialmente em países com menores índices de desenvolvimento. A utilização de ferramentas para auxílio no cuidado do paciente diabético e para melhor alocação de recursos do sistema de saúde é fundamental e amplamente recomendada. Neste contexto, a telemedicina surge como alternativa bastante atual para suporte ao manejo do DM2 e para construção de uma rede de saúde mais efetiva e racional.

Os delineamentos de estudo com reconhecida qualidade são as revisões sistemáticas com metanálise e os ensaios clínicos randomizados (ECR), sendo menos suscetíveis a vieses de seleção e outros fatores de confusão, permitindo-se tirar conclusões e criar evidências sólidas. Utilizando-se destes recursos, analisamos nesta tese, a eficácia de uma ferramenta de telemedicina (ligações telefônicas) no controle glicêmico do paciente com DM2 através de metanálise de ECRs com Trial Sequential Analysis (TSA), e avaliamos ainda, por meio de um ECR, a sua importância no auxílio à contrarreferência destes pacientes para a atenção primária.

Em relação à eficácia das ligações telefônicas no controle glicêmico do DM2, por meio de metanálise, se observa uma melhora numérica da HbA1c, principalmente quando a intervenção envolvia a participação de enfermeiras e quando as ligações telefônicas incluíam alteração do tratamento farmacológico. No entanto, os resultados não apresentaram estabelecida relevância clínica e os estudos incluídos eram bastante heterogêneos, limitando a consistência dos achados e apontando a necessidade de estudos mais detalhados e bem delineados. Analisando, por meio de ensaio clínico randomizado, o papel das ligações telefônicas no controle glicêmico dos pacientes com DM2 bem controlado e sem complicações crônicas graves submetidos à alta de serviço terciário para a atenção primária, não se verifica benefício desta intervenção. Porém, observa-se que os mesmos pacientes se mantêm no alvo glicêmico

recomendado, tornando segura a alta ambulatorial de serviço especializado para a atenção primária.

De forma agregada, estes achados contribuem para o conhecimento da utilização da telemedicina no cuidado dos pacientes com DM2. Além disso, apontam aspectos ainda não explorados e passíveis de melhor investigação.