UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:

CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

TESE DE DOUTORADO

Associação do Treinamento Físico Estruturado e Recomendação de Atividade Física com o Controle Glicêmico em Pacientes com Diabetes Tipo 2

Aluno: Daniel Umpierre de Moraes

Orientador: Prof. Dr. Jorge Pinto Ribeiro

Porto Alegre, março de 2012.

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Orientador:
Prof. Dr. Jorge Pinto Ribeiro

Banca Examinadora:
Prof. Dr. Pedro Curi Hallal
Prof. Dr. Luís Henrique Santos Canani
Profa. Dra. Sandra Cristina P. Costa Fuchs

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ÍNDICE

1. INTRODUÇÃO

O diabetes mellitus é uma condição de etiologia multifatorial e se relaciona com risco aumentado para o desenvolvimento de complicações metabólicas, neurológicas e/ou cardiovasculares, as quais contribuem para uma elevada morbi-mortalidade relacionada à gravidade da doença.[1] Dados da população do Estado do Rio Grande do Sul indicam uma prevalência aparentemente superior àquela da população brasileira.[3,4]

O estilo de vida modernizado contribui para o desenvolvimento de diabetes, e há projeções de um aumento importante na incidência do diabetes tipo 2, que se associa mais diretamente com obesidade e sedentarismo – fatores fortemente relacionado ao desenvolvimento da doença.[5] Neste contexto, a prática regular de atividade física pode contribuir para a prevenção primordial do DM, assim como ser utilizada como terapia complementar no tratamento dos pacientes com DM. Embora diversas estratégias sejam possíveis para a promoção e/ou aplicação do exercício físico, poucos estudos têm abordado uma análise mais abrangente dos efeitos induzidos por cada tipo de exercício ou por diferentes prescrições de treinamento físico.

Portanto, o presente documento inicialmente descreve o marco teórico sobre diabetes tipo 2 e exercício físico, abordando particularmente os efeitos promovidos por pelo exercício físico na prevenção e tratamento da diabetes tipo 2. Em capítulos subseqüentes, serão apresentados dois estudos que buscam sumarizar os efeitos de diferentes abordagens para realização de exercício, assim como avaliar a influência de características do treinamento físico sobre os níveis glicêmicos de pacientes com diabetes tipo 2.

2. REVISÃO DE LITERATURA

O Diabetes Mellitus (DM) é uma doença crônico-degenerativa caracterizada por hiperglicemia crônica, na qual os pacientes apresentam complicações crônicas e elevada morbi-mortalidade decorrente das mesmas.[1] Trata-se de importante problema de saúde pública mundial, sendo uma das principais causas de morbi-mortalidade também no Brasil.[2] No ano de 1992, os dados de um estudo multicêntrico, onde teste oral de tolerância à glicose foi utilizado para levantamento da prevalência de DM no Brasil, demonstraram uma prevalência geral de 7,6% na população de 39 a 69 anos.[3] Mais recentemente, um estudo transversal de base populacional realizado no Estado do Rio Grande do Sul, no qual glicemia plasmática de jejum foi o método utilizado para escaneamento, indicou 12,4% para a prevalência de diabetes, e 7,4% para tolerância à glicose diminuída.[4] Atualmente 285 milhões de pessoas apresentam DM no mundo e estima-se que o número de indivíduos com DM deverá aumentar para 439 milhões de adultos até 2030.[5]

As complicações clínicas relacionadas ao DM determinam elevados custos de tratamento, bem como a redução de produtividade laboral, o que é problema adicional decorrente da doença. Uma análise recente[6] revelou que o custo anual do paciente com DM no Brasil é de aproximadamente US$ 2.108,00, o que atualmente se aproxima de R$ 3.700,00 por paciente. Cabe ressaltar que os custos têm um aumento considerável de acordo com a gravidade da doença, com a expressiva influência de complicações vasculares apresentadas por no DM.[6] Neste sentido, estimativas conservadoras da Organização Mundial da Saúde sugerem que, entre 2006 e 2015, somente três doenças crônico-degenerativas (DM, cardiopatia isquêmica e doença cerebrovascular) ocasionarão ao Brasil uma importante perda econômica na ordem de US$ 4,18 bilhões,

devido à menor capacidade de trabalho, aposentadorias por invalidez, e custos associados aos tratamento.[7]

As complicações crônicas do DM podem provocar conseqüências bastante prejudiciais, e muitas destas são fisiologicamente irreversíveis. Em longo prazo, estas complicações levam a manifestações clínicas decorrentes de dano, disfunção e falha de diversos órgãos e tecidos - especialmente rins, olhos, nervos, coração e vasos sanguíneos. Estas complicações podem ser divididas em macrovasculares (doença arterial coronariana, doença vascular periférica, doença cerebrovascular) e microvasculares (nefropatia, retinopatia diabética e neuropatia). Sua prevalência dentre pacientes com DM é elevada, o que já foi mostrado objetivamente em nosso meio.[8] No Brasil, um registro nacional para DM e hipertensão arterial, com mais de 1,6 milhões de pacientes com DM acompanhados, mostrou que 4,3% desta amostra desenvolveu pé diabético; 2,2% dos pacientes tiveram amputação prévia; 7,8% tiveram doença renal; 7,8% sofreram infarto agudo do miocárdio; e 8,0% foram vitimados por acidente vascular cerebral. Na análise destes dados juntamente com os registros de óbitos, há evidências de expressiva mortalidade atribuível ao DM, onde a taxa de morte ajustada por idade e gênero é 57% maior em indivíduos com DM quando comparados à população em geral.[2]

A hemoglobina glicada (HbA1c) é um importante marcador do controle glicêmico em pacientes com DM. Mais recentemente, tem sido também utilizada para o diagnóstico de DM, onde níveis iguais ou superiores a 6,5% indicam a presença da doença.[9] O DM tipo 2 (DM2) é responsável por aproximadamente 90% dos casos de DM e caracteriza-se por ser uma desordem de etiologia complexa, resultante de fatores genéticos e ambientais. Pessoas com mais de 30 anos usualmente são as mais afetadas por este tipo de condição, mas alta ingesta calórica associada ao baixo gasto calórico

pode predispor à obesidade e desenvolvimento precoce da DM2.[1] Embora exista um forte sinergismo entre vários genes que influenciam a resistência à insulina e a capacidade para secreção deste hormônio, os fatores ambientais como dietas hipercalóricas, obesidade, sedentarismo e idade parecem influenciar muito o desenvolvimento de DM2.[10-12] Dentre as principais alterações fisiológicas que influenciam a gênese da hiperglicemia no DM2, podem-se citar: aumento da produção hepática de glicose, diminuição na secreção e ação da insulina, e redução da utilização e armazenamento de glicose.

O tratamento da DM2 compreende a educação do paciente para cuidados gerais e auto-manejo, adoção de dieta apropriada, adesão ao tratamento farmacológico, e a prática de exercícios físicos estruturados.[1] Após o diagnóstico, a terapia com metformina é iniciada (a menos que haja contra-indicação) juntamente com intervenções de estilo de vida (em particular, dieta e atividade física). Entretanto, a piora nos níveis glicêmicos pode ocorrer em um prazo de 2 a 3 anos, e portanto combinação medicamentosa em geral é necessária.[13]

Neste sentido, a adição individual de tiazolidinedionas, sulfoniluréias, glinidas, análogos do peptídio semelhante ao glucagon (GLP-1), inibidores de alfa-glicosidase ou inibidores da dipeptidil peptidase 4 (DPP-4) à terapia agressiva de metformina (1500 mg/dia, ou dose máxima tolerada sendo $\geq$ 1000 mg/dia) associa-se com redução de 0,64 a 0,97% nos níveis absolutos de HbA1c, comparados ao placebo.[14] Quando um terceiro medicamento (insulina, glitazonas, acarbose, análogos de GLP-1, ou inibidores de DPP-4) é adicionado com terapia vigente de metformina e sulfoniluréia, a redução absoluta de HbA1c encontra-se entre 0,7% (para acarbose) e 1,08% (para insulina), em comparação com placebo.[15] Observa-se que a melhora no controle glicêmico é semelhante entre os diferentes antidiabéticos, tanto como segunda droga,[14] como na

adição como terceira droga.[15] No entanto, há diferenças quanto aos efeitos adversos das diferentes opções, havendo aumento de peso e de hipoglicemias com as sulfoniluréias e insulina, o que não é desejável para estes pacientes.[14, 15]

Ainda que as combinações farmacológicas possam proporcionar o controle glicêmico em diferentes estágios do DM2, diversas evidências indicam que mudanças no estilo de vida podem adicionar benefícios no tratamento da doença.[15-19] Estudo que avaliou a influência da dieta saudável e exercícios físicos sobre o controle glicêmico e fatores de risco cardiovascular, 652 pacientes com DM2 – em uso de insulina (N=212), hipoglicemiantes orais (N=197), ou sem medicação apesar de glicose plasmática acima de 140 mg/dl (N=243) – participaram de um programa envolvendo exercício aeróbico por até 2 horas por dia, e dieta rica em fibras e com baixos conteúdos de gordura. Após o programa, que durou somente 26 dias, os participantes apresentaram a redução média de 15% nos valores de glicose plasmática, o que também foi acompanhada por modificações em outros fatores de risco, como pressão arterial, colesterol total e triglicerídeos.[20] Além disto, 39% dos pacientes que usavam insulina puderam cessar a medicação, enquanto 71% dos pacientes em uso de antidiabéticos orais puderam descontinuar os medicamentos. Ainda que o trabalho possa ser criticado pelo uso de uma dieta bastante restritiva e realização diária de exercício físico, os quais são difíceis de serem mantidos no médio e longo prazo, seus resultados reforçam o consenso atual[1] de que a realização de exercício físico e o planejamento da dieta, juntamente com metformina, representam a primeira linha de tratamento da doença.

2.1 Estilo de Vida e Diabetes Tipo 2

Conforme introduzido anteriormente, fatores ambientais desempenham um papel importante para o aparecimento de DM2. Isso pode ser constatado na população da China, que em um período de 10 anos teve aumento de três vezes na prevalência de DM2 em virtude da adoção de hábitos ocidentais de alimentação e massivo desenvolvimento tecnológico e industrialização.[21] Por outro lado, norte-americanos japoneses que conservaram um estilo de vida oriental, apresentaram redução da prevalência de DM2.[22] Adicionalmente, em um estudo com 84.891 mulheres acompanhadas por 16 anos, aproximadamente 90% dos novos casos (de um total de 3.300 diagnosticados) de DM2 puderam ser atribuídos a fatores como falta de atividade física, dieta, obesidade e tabagismo.[23]

O risco para o desenvolvimento de DM2 se associa diretamente ao grau de obesidade em homens e mulheres. Em uma coorte com 5 anos de seguimento de mais de 20.000 homens médicos, o risco triplicou quando o índice de massa corporal (IMC) era superior a 26,4 kg/m^2.[24] De forma similar, um estudo[25] com 114.281 mulheres seguidas por 14 anos indicou, através de análises ajustadas para a idade, que o IMC foi o principal preditor para o risco de DM2. Neste cenário, a obesidade na região visceral parece ter uma estrita relação com o aumento da resistência à insulina, a qual representa o principal fator fisiopatológico no desenvolvimento de DM2. Embora o mecanismo de resistência à insulina não esteja complemente elucidado, o tecido adiposo produz citocinas (leptina, fator de necrose tumoral) e ácidos graxos que comprometem a secreção e ação da insulina. Adicionalmente, subprodutos da metabolização dos ácidos graxos inibem a fosforilação do substrato do receptor de insulina 1 (IRS-1) em tirosina e estimulam sua fosforilação em serina, prejudicando a sinalização intracelular da cascata insulínica.[26]

A inatividade física também contribui substancialmente para a incidência de DM2. Evidências de uma coorte com seguimento de 37.918 homens por 10 anos indicam que a atividade sedentária, mensurada pela quantidade de tempo em que se assistia televisão, se associa positivamente com o risco para incidência de DM2, mesmo após ajustes para níveis de atividade física, IMC e variáveis da dieta.[27] De fato, sujeitos saudáveis não-obesos sofrem redução da sensibilidade à insulina em somente 10 dias de inatividade física, o que parece ser mais pronunciado em indivíduos saudáveis sem história familiar de DM2, os quais apresentaram redução de aproximadamente 37% na sensibilidade à insulina. Para indivíduos com história familiar de DM2, a inatividade física ainda leva ao aumento da inflamação de baixo grau, caracterizada por redução em adiponectina (que possui propriedades anti-inflamatórias, anti-diabéticas e anti-aterogênicas), e aumento de fator de necrose tumoral alfa (potente mediador pró-inflamatório associado com resistência à insulina), os quais ocorrem mesmo sem alteração do peso corporal.[28]

Um trabalho recente com uso de acelorômetros para quantificação do nível de atividade física, mostrou que o nível de inatividade física se relacionou progressivamente com variáveis metabólicas de pacientes que receberam diagnóstico de DM2 nos 6 meses anteriores ao estudo.[29] Em análise transversal por modelos de regressão, os autores demonstraram que mais tempo em atividades sedentárias associou-se com aumentos na circuferência da cintura, e resistência à insulina avaliada pelo índice HOMA-IR.[29] Por outro lado, pausas nos períodos sedentários estiveram associadas a menores valores de circunferência da cintura, e uma fraca associação linear com níveis de colesterol HDL.[29]

Diversos relatos demonstram a associação de níveis aumentados de atividade física com menor incidência de DM2. Neste cenário, um estudo[30] com 5.990 homens

seguidos por 14 anos indicou que para cada aumento de 500 calorias no gasto energético semanal em atividades físicas (caminhar, correr, subir escadas, etc.) no tempo livre, há uma redução de 6% no risco de DM2. Isto parece ser ainda mais pronunciado nos sujeitos em alto risco para desenvolvimento da doença, os quais foram classificados de acordo com história familiar para hipertensão arterial, diabetes e com IMC acima de 25 kg/m².[30] Este padrão de maior proteção através do exercício regular nos indivíduos de alto risco também foi encontrado em uma coorte[24] com 21.271 homens seguidos por 5 anos. Nesta análise[24], a redução da incidência de DM2 ajustada para IMC e idade foi progressiva e ocorreu de acordo com a freqüência semanal e intensidade de exercício reportadas pelos sujeitos (RR= 0,71; IC 95%, 0,56 – 0.91), comparando uma sessão de exercício físico por semana com menos de uma sessão de exercício por semana).

Maiores níveis de atividade física também conferem proteção para DM em mulheres. Em uma coorte contemporânea com mais de 70.102 mulheres acompanhadas por 4 anos, pesquisadores do *Nurses' Health Study* encontraram risco relativo para o desenvolvimento de DM2 ajustado em análise multivariada de 0,41 (IC 95%, 0,33 – 0,52) para mulheres que tinham maiores quantidades ou velocidades de caminhada, em comparação a mulheres que relataram marcha em baixas velocidades.[31] É importante notar que o risco de desenvolvimento de DM2 também está reduzido de acordo com a capacidade cardiorrespiratória, que possui uma mensuração mais objetiva do que o nível de atividade física. Através deste marcador, indivíduos com baixo condicionamento cardiorrespiratório (média: 9,3 ± 0,9 METs) apresentaram risco 3,7 vezes maior para diagnóstico de DM2, quando comparados aos indivíduos com melhor condicionamento (média: 13,7 ± 1,2 METs).[32]

2.2 Recomendação de Atividade Física e Diabetes Tipo 2

A partir dos consistentes indícios de menor incidência de DM2 em indivíduos ativos, ensaios clínicos randomizados têm sido conduzidos para testar se intervenções de atividade física poderiam prevenir ou retardar o aparecimento do DM, ou, ainda, mostrarem eficácia para o controle glicêmico de pacientes com DM2 já estabelecida. Por definição, atividade física é qualquer movimento corporal proveniente de contração muscular e que resulte em gasto energético acima da condição de repouso.[33] Em intervenções com recomendação de atividade física, usualmente não há supervisão profissional durante a prática do exercício, ou seja, o indivíduo recebe uma orientação para praticar exercício físico, mas o realiza de forma livre, espontânea, com um programa flexível e não estruturado (por exemplo, caminhada de 3 a 5 vezes por semana, de 30 a 40 min, em uma intensidade que "aumente a respiração").

No estudo *Diabetes Prevention Program* (DPP), 3.234 sujeitos com pré-diabetes foram randomizados para uma de três intervenções: 1) aconselhamento intensivo para atividade física e nutrição (grupo "estilo de vida"); 2) terapia farmacológica com metformina; ou 3) grupo placebo.[34] Após aproximadamente 3 três anos de seguimento, o grupo de estilo de vida apresentou redução de 58% na progressão para DM2, comparado a 31% de redução no grupo que recebeu metformina.[34] Cabe salientar um aspecto bastante positivo do estudo DPP, que foi o sucesso da adesão dos indivíduos à prática de atividade física, visto que 74% do grupo de estilo de vida realizou atividade física por pelo menos 150 minutos por semana.

Apesar de consistentes benefícios para a prevenção da incidência de DM2, os efeitos da recomendação de atividade física sobre o controle glicêmico são menos claros. Neste sentido, um ensaio clínico randomizado em pacientes com DM2 apontou que a recomendação de atividade física, com freqüência indicada de 2 vezes por semana

e sem associação a outras medidas de estilo de vida, induziu uma diminuição na resistência à insulina (mensurada por HOMA-IR), mas não foi suficiente para modificar os níveis de HbA1c após 12 meses de intervenção.[35]

O aconselhamento para realização de exercício físico não supervisionado apresenta algumas vantagens práticas relacionadas à possibilidade de implementação no nível comunitário/populacional, como possíveis custos reduzidos quando comparado a programas supervisionados, e flexibilidade de cronograma para que os indivíduos alcancem as metas propostas. Dentre as principais limitações, podem-se citar: adesão dos indivíduos ao aconselhamento, manutenção das medidas de estilo de vida no médio e longo prazo, e verificação/monitoramento do nível de aderência ao total de sessões propostas em determinado período.

Para controlar algumas limitações do aconselhamento de atividade física, Tudor Locke e colaboradores realizaram um estudo com uma fase presencial para início das atividades do estudo, que envolveu não somente com as instruções para exercícios físicos, mas também com a mensuração dos níveis de atividade física através do uso de acelerômetros.[36] Embora a intervenção tenha produzido um aumento da realização de exercício em aproximadamente 30 minutos por dia (3.369 passos/dia) após 24 semanas de intervenção, o grupo que seguiu tais recomendações de estilo de vida apresentou níveis similares de HbA1c, em comparação ao grupo controle. No entanto, a análise combinada dos grupos indicou uma associação inversa entre número de passos por dia e os níveis de glicose plasmática em jejum (r=-0,45, P=0,001) e HbA1c (r=-0,42, P=0,003).

Intervenções mais abrangentes e/ou intensivas para mudança do estilo de vida parecem apresentar maior influência sobre o controle glicêmico dos pacientes com DM2. Neste particular, um ensaio clínico randomizado que utilizou exercício não

estruturado (sem prescrição específica) em grupo e forneceu material impresso com 20 recomendações genéricas para controle da dieta, demonstrou uma redução média de 1.2% (percentis 25% e 75%: -1,30 e 0,3%) nos níveis absolutos de HbA1c após 12 meses de intervenção.[37]

Mais recentemente, um ensaio clínico multicêntrico com 5.145 pacientes com DM2 randomizados para dieta associada a atividade física, ou para educação em diabetes, reforçou as evidências de que intervenções combinadas para o estilo de vida podem proporcionar maior benefício metabólico.[38] Após 12 meses de estudo, os pacientes alocados no grupo de restrição calórica para redução de 7% do peso corporal inicial associada à recomendação de atividade física de 175 minutos por semana demonstraram redução de aproximadamente 0,7% nos níveis absolutos de HbA1c.[38] Embora o seguimento de 4 anos do estudo demonstre uma menor magnitude na diminuição de HbA1c, sendo -0,36% em comparação à mensuração de pré-estudo, este efeito no controle glicêmico permanece sigficativo e soma-se de benefícios no peso corporal e condicionamento físico (-7% e +12%, respectivamente, em comparação aos valores pré-estudo).[18]

Por fim, de acordo com uma análise de 10.352 indivíduos, aqueles que realizaram no mínimo uma atividade física por semana no tempo de lazer apresentaram menores taxas de mortalidade por qualquer causa (HR=0,74; IC 95%, 0,67 – 0,81) e mortalidade cardiovascular (HR=0,71; IC 95%, 0,62 – 0,82), quando comparados aos seus pares inativos.[39] Um aspecto importante é que esta proteção associada com a atividade física parece ocorrer independentemente do nível de HbA1c, sendo verificado tanto em sujeitos normoglicêmicos ou com DM2 pré-existente, sugerindo importância da recomendação de atividade física para redução de desfechos duros em diferentes condições metabólicas. No entanto, os dados conflitantes sobre a efetividade do

aconselhamento de exercício para o controle glicêmico em pacientes com DM2 ainda demonstram que o conhecimento sobre tal intervenção encontra-se limitado e será beneficiado por estudos futuros.

2.3 Treinamento Físico Estruturado

As intervenções programadas de exercício físico são classicamente as mais estudadas em diferentes condições patológicas. Tais programas são denominados como treinamento físico estruturado, e diferenciam-se da recomendação de atividade física por apresentarem um planejamento para todo o período de intervenção, prescrições específicas e/ou individualizadas, e na maioria das vezes supervisão profissional a cada sessão de treinamento. Dessa forma, uma desvantagem está relacionada ao maior custo em comparação às estratégias que utilizam somente o aconselhamento para o exercício. Por outro lado, o treinamento estruturado possibilita um controle mais estrito sobre as variáveis da prescrição (por exemplo, duração e intensidade), bem como os pacientes geralmente atendem a um maior número de sessões.

No tratamento não-medicamentoso consistindo de exercício estruturado para pacientes com DM2, três principais variações de treinamento físico estruturado têm sido utilizadas: treinamento aeróbico, treinamento resistido e treinamento combinado (exercícios aeróbicos e resistido em uma mesma sessão). Em sub-tópicos seguintes, iremos apresentar brevemente os efeitos metabólicos e mecanismos de ação de cada tipo de treinamento.

2.3.1 Treinamento Aeróbico

O treinamento aeróbico consiste de movimentos contínuos (por exemplo, caminhada, corrida, ciclismo) geralmente realizados com grandes grupamentos

musculares e mantidos por média ou longa durações, as quais usualmente situam-se entre 20 a 90 minutos. Em relação à homeostase da glicose, trabalhos clássicos demonstram que uma única sessão de exercício aeróbico promove aumento da sensibilidade à insulina em sujeitos saudáveis, obesos, ou com DM2.[40-42]

O principal mecanismo para o aumento na captação aguda de glicose durante o exercício é a translocação do transportador de glicose 4 (GLUT4) para a membrana plasmática celular.[43] Este processo pode ser induzido diretamente por contrações musculares, por via de sinalização diferentes daquela através da qual a insulina medeia o transporte de glicose.[44-46] Apesar da expressão normal de GLUT4 no músculo esquelético de pacientes com DM2[47, 48], estes exibem uma resposta muscular atenuada em resposta à insulina, resultando em atenuada captação de glicose.[49, 50] Em contrapartida, uma única sessão de 45 a 60 minutos de exercício aeróbico aumenta a translocação celular de GLUT4 de forma similar em pacientes com DM2 e sujeitos controles sem DM2.[51]

Estudos com diferentes protocolos de treinamento indicam que o exercício aeróbico crônico reduz a resistência à insulina em diversas populações, incluindo sujeitos idosos[52], não-obesos[53], com sobrepeso ou obesidade[54], e em indivíduos com DM2.[55] Adicionalmente, um recente estudo[56] com somente 7 dias de exercício aeróbico, 60 minutos por dia, em intensidade moderada (60 a 75% da freqüência cardíaca de reserva), demonstrou que pacientes com DM2 apresentaram reduções na freqüência, magnitude e duração de excursões glicêmicas. Esses efeitos podem ser parcialmente mediados por aumento na sensibilidade e responsividade periféricas à insulina, bem como atenuação na produção hepática de glicose[57], o que sugere que as adaptações

induzidas pelo treinamento aeróbico em diversas variáveis metabólicas nos pacientes com DM2 podem ser iniciadas no curto prazo.

Estudos com treinamento físico para o tratamento do DM2 têm crescentemente definido a HbA1c como desfecho primário para as intervenções, e reportam que as reduções nos níveis de HbA1c podem ocorrer a partir de 12 semanas de intervenção.[58-60] Revisões sistemáticas de estudos com treinamento aeróbico indicam, através de meta-análises, que esta intervenção reduz em aproximadamente 0,6% os níveis absolutos de HbA1c.[61-63] Ainda, os benefícios no controle glicêmico parecem ser manifestados independentemente de alterações em outros fatores de confusão, como peso corporal.[64,65]

As características da prescrição de exercício físico podem influenciar os efeitos cardiorrespiratórios e metabólicos promovidos pelo treinamento físico em pacientes com DM2. Neste cenário, uma meta-análise realizada por Boulé e colaboradores[66] sumarizou estudos com diferentes intensidades de treinamento aeróbico e seus respectivos efeitos sobre o consumo máximo de oxigênio (VO_2max) e HbA1c. O trabalho sugere que maiores intensidades de exercício promovem maior adaptação cardiorrespiratória (representada pelo incremento no VO_2max) e se associam com menores níveis de HbA1c após as intervenções.[66] Por outro lado, o volume de exercício (o qual indica a quantidade de exercício) não se associou com as alterações nas variáveis de interesse.[66] Estes achados divergem daqueles encontrados em um estudo[54] que randomizou indivíduos obesos não-diabéticos para três combinações de intensidade e volume de treinamento de caminhada: 1) baixo volume (19km por semana) e moderada intensidade (40-55% do VO2max); 2) baixo volume (19km por semana) e alta intensidade (65-80% do VO2max); e 3) alto volume (32km por semana) e alta intensidade (65-80% do VO2max). Neste trabalho, as três diferentes intervenções

promoveram aumento na sensibilidade à insulina, no entanto, os maiores benefícios metabólicos ocorreram nos sujeitos que seguiram uma prescrição com maior volume semanal de exercício.[54] Adicionalmente, um estudo recente indicou que pacientes com DM2 obtiveram reduções similares nos níveis de HbA1c após treinamento aeróbico contínuo em intensidade baixa a moderada (50% do VO2max), ou treinamento aeróbico intervalado de moderada a alta intensidade (75% do VO2max).[67]

Em suma, o exercício aeróbico tem sido bastante estudado em relação aos fatores que influenciam o controle metabólico e ação insulínica em diferentes populações. De forma importante, os efeitos também ocorrem em pacientes com DM2, especialmente através da diminuição de HbA1c, o que é constatável em diferentes revisões sistemáticas com meta-análises.

Embora o controle glicêmico possa ser afetado por variações na prescrição de treinamento físico, ainda há dados conflitantes sobre as características de exercício que podem ser mais benéficas para o controle metabólico no DM2.

2.3.2 Treinamento Resistido

O treinamento resistido, também denominado como treinamento de força ou musculação, consiste de movimentos realizados contra resistências externas (exemplo: pesos). Alguns dos mecanismos propostos para o controle metabólico induzido por este tipo de treinamento compreendem: diminuição de gordura subcutânea e visceral, redução da resistência à insulina, e aumento de massa muscular (e conseqüentemente do gasto energético).[68]

Estudos que analisaram os efeitos agudos do exercício resistido têm demonstrado resultados que ainda não estabelecem especificamente o mecanismo para o aumento da captação de glicose. Análises da captação de glicose induzida por uma

única sessão de exercício resistido mostraram que os processos de fosforilação de proteínas (AS160) que sinalizam a translocação de GLUT4 para a membrana celular estão diminuídos imediatamente após uma sessão típica com exercícios de força, o que é acompanhado por redução concomitante na ação da insulina.[69] Porém, um estudo posterior sugeriu que o aumento na captação de glicose pode ocorrer em até 2 horas após a sessão, o que foi acompanhado de maior atividade da AMPK (proteína quinase ativada por AMP) – uma importante reguladora na translocação de GLUT4 induzida por contrações musculares.[70]

No médio e longo prazos, o treinamento resistido parece aumentar o conteúdo de GLUT4 e conseqüentemente a ação da insulina em diferentes populações.[71-73] Neste sentido, indivíduos com DM2 não-obesos apresentaram aumento de 48% na taxa de desaparecimento da glicose, indicando maior ação insulínica após 6 semanas de treinamento composto por 9 exercícios de musculação.[71] O aumento da massa livre de gordura representa uma das hipóteses para a melhora do controle glicêmico a partir do treinamento resistido, visto que induz a um aumento no tecido metabolicamente ativo. Entretanto, de acordo com um estudo com 90 dias de treinamento resistido, seguidos de 90 dias de destreinamento (sem prática de exercício), Andersen e colaboradores demonstraram que o aumento da captação sistêmica de glicose não se correlaciona com alterações na massa muscular (avaliada por ressonância nuclear magnética).[74] Isto indica que esta forma de exercício oferece uma estratégia para diminuição da resistência à insulina, que é manifestada mesmo na ausência de outras mudanças de condicionamento físico, como aumento de massa muscular ou do VO_2max.

Em termos das características da prescrição do exercício resistido, protocolos de treinamento[75] com uso de baixa a moderada intensidade (40 a 60% da carga máxima) promoveram aumento na ação da insulina de 23 a 48%, porém, idosos submetidos a

treinamento[76] em intensidade de 70 a 85% da carga máxima não demonstraram alterações nas taxas de desaparecimento de glicose após 16 semanas de intervenção. Mais recentemente, um ensaio clínico randomizado[77] evidenciou redução média de 1,2% nos níveis absolutos de HbA1c em idosos com DM2 que realizaram treinamento resistido de alta intensidade (75 a 85 % da carga máxima) por 6 meses. Ainda que os resultados deste estudo estejam suscetíveis à influência de uma intervenção de dieta que foi associada ao treinamento físico, outros ensaios clínicos confirmam os benefícios deste tipo de treinamento no controle glicêmico de pacientes com DM2.[65, 78]

Por fim, há uma carência de estudos que sumarizem os efeitos do treinamento resistido, quando aplicado de forma exclusiva, sobre os níveis de HbA1c em indivíduos com DM2. Em uma revisão sistemática que incluiu e descreveu separadamente estudos com treinamento resistido, a meta-análise dos ensaios demonstrou redução de 0,6% na HbA1c.[62] Ainda que tal benefício possa ser comparado àquele induzido pelo treinamento aeróbico[61, 63], é importante ressaltar que a análise combinou estudos com diferentes intervenções (aeróbicas e resistidas), e assim não esclarece o efeito isolado do treinamento de força. No entanto, o número crescente de ensaios clínicos com treinamento resistido possibilita uma análise combinada destes estudos, o que poderia contribuir para recomendações mais específicas para a realização de exercícios de força em indivíduos com DM2.

2.3.3 Treinamento Combinado

O treinamento combinado consiste na realização de exercícios aeróbicos e resistidos, que podem se complementar em uma mesma sessão de exercício, ou ainda serem distribuídos ao longo da programação semanal de treinos. Este tipo de treinamento oferece potenciais benefícios que se expressam tanto em variáveis

cardiorrespiratórias (induzidas pelo componente aeróbico do treinamento), como também em qualidades neuromusculares (induzidas pelo componente resistido). Portanto, esta estratégia mostra-se interessante para indivíduos que necessitam de incrementos não só no VO_2, mas também em força e resistência muscular (por exemplo, idosos com DM2).

A combinação de exercícios aeróbicos e de força para pacientes com DM2 foi inicialmente testada em um ensaio clínico randomizado através de uma intervenção de 16 semanas para 28 mulheres obesas no período pós-menopausa.[79] Apesar dos resultados terem indicado aumento na sensibilidade à insulina, redução em peso corporal e gordura abdominal, os pesquisadores não encontraram alterações nos níveis de HbA1c.[79] No entanto, um estudo foi posteriormente planejado especificamente para testar o efeito do treinamento combinado, e assim randomizou 251 pacientes com DM2 para uma das quatro intervenções seguintes: 1) grupo controle sem exercício; 2) treinamento aeróbico; 3) treinamento resistido; ou 4) treinamento combinado.[65] Como esperado, após 6 meses de estudo, os grupos de treinamento aeróbico e resistido aplicados isoladamente reduziram os valores de HbA1c em comparação ao grupo controle. Porém, os efeitos foram mais pronunciados no grupo que realizou treinamento combinado, que por sua vez induziu uma diminuição absoluta de 0,95% nos níveis de HbA1c.[65] Embora tais resultados sugiram interessantes efeitos aditivos dos diferentes componentes (aeróbico e resistido) do treinamento combinado, esta interpretação é limitada pelo fato de que este braço do estudo compreendeu os programas completos de treinamento aeróbico e resistido, portanto contendo o dobro de volume (quantidade) de exercício.

Recentemente, um ensaio clínico randomizado foi desenhado para equiparar os volumes dos treinamentos aeróbico, resistido, e combinado, os quais foram realizados

por pacientes com DM2 por uma duração total de 9 meses.[80] Neste estudo, a análise por intenção de tratar indicou uma modesta redução de 0,34% nos valores absolutos de HbA1c dos pacientes que realizaram treinamento combinado. Além da magnitude do efeito ser bastante diferente daquele encontrada anteriormente por Sigal e colaboradores[65], os grupos que realizaram somente treinamento aeróbico ou resistido não apresentaram melhora no controle glicêmico. Alguns fatores podem ter influenciado os resultados neutros das intervenções de exercício aeróbico ou resistido, entre eles incluem-se: baixo volume semanal de exercícios (aproximadamente 140 minutos), níveis baixos de HbA1c no início da intervenção, e limitado tamanho amostral para detecção de diferenças inter-grupos.

O treinamento combinado representa uma atrativa estratégia para melhora de diferentes variáveis da saúde dos pacientes com DM2. Entretanto, dois grandes ensaios clínicos randomizados indicam marcadas diferenças na magnitude do efeito sobre a HbA1c, o que pode ser bastante influenciado por diferentes características das prescrições de treinamento físico. Além disso, uma análise combinada dos diferentes estudos disponíveis na literatura poderia contribuir para esclarecer se o treinamento combinado pode demonstrar maior associação com a melhora do controle glicêmico no DM2.

Em síntese, há diversas evidências indicando que a captação de glicose é diretamente estimulada pela realização de exercício físico. Em curto prazo, estes efeitos promovem melhora na ação da insulina. No longo prazo, isto se traduz na eficácia do treinamento físico supervisionado – aeróbico, resistido, ou combinado – para o controle glicêmico de pacientes com DM2. Entretanto, ainda é bastante incipiente o conhecimento da magnitude de redução nos níveis de HbA1c produzida por diferentes intervenções de exercício em pacientes com DM2. Além disso, embora variáveis de

treinamento físico possam impactar diferentemente nas adaptações metabólicas, estes fatores de prescrição de exercício ainda são pouco explorados nos programas para pacientes com DM2.

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3. OBJETIVOS

Os objetivos listados abaixo estão divididos de acordo com os estudos que serão apresentados nos capítulos seguintes.

3.1 Estudo 1

Objetivo geral

Avaliar a associação de programas de treinamento físico estruturado (consistindo de exercícios aeróbicos, resistidos e da combinação de ambos) e da recomendação de atividade física com as alterações nos níveis de hemoglobina glicada em pacientes com diabetes tipo 2.

Objetivos específicos

- Conduzir uma revisão sistemática com meta-análise para quantificação dos efeitos do treinamento aeróbico, resistido, e combinado sobre os níveis absolutos de hemoglobina glicada;

- Conduzir uma revisão sistemática com meta-análise para quantificação dos efeitos da recomendação de atividade física com e sem intervenções de dieta sobre os níveis de hemoglobina glicada;

- Realizar modelos de meta-regressão para identificar variáveis associada com a heterogeneidade de resultados dos estudos incluídos;

- Realizar análises de sensibilidade para estratificação de estudos de acordo com variáveis que possam exercer influência sobre a associação das intervenções de exercício ou atividade física com os níveis de hemoglobina glicada.

3.2 Estudo 2

Objetivo geral

Avaliar a associação das características de volume e intensidade de exercício em programas de treinamento físico aeróbico, resistido e combinado com as alterações nos níveis de hemoglobina glicada em pacientes com diabetes tipo 2.

Objetivos específicos

- Conduzir uma revisão sistemática com meta-análise para quantificação dos efeitos do treinamento aeróbico, resistido e combinado sobre as variações absolutas de hemoglobina glicada;

- Extrair variáveis específicas de volume (quantidade) e intensidade (nível de esforço) em cada tipo de treinamento físico para posterior associação com os efeitos gerados na meta-análise;

- Através das estimativas de efeitos geradas na meta-análise, realizar modelos de meta-regressão para identificar aspectos clínicos e características de cada tipo de treinamento físico que contribuem para a heterogeneidade dos resultados entre os estudos individuais;

- Através da identificação de variáveis de interesse nos modelos de meta-regressão, avaliar a correlação entre o volume e intensidade nos diferentes tipos de treinamento físico com os respectivos efeitos sobre os níveis de hemoglobina glicada.

ARTIGO I

Physical Activity Advice Only or Structured Exercise Training and Association with HbA_{1C} Levels in Type 2 Diabetes

A Systematic Review and Meta-analysis

Recomendação de Atividade Física ou Treinamento Físico Estruturado e Associação com Níveis de HbA_{1C} no Diabetes Tipo 2

Revisão Sistemática e Meta-análise

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Physical Activity Advice Only or Structured Exercise Training and Association with HbA_{1C} Levels in Type 2 Diabetes: A Systematic Review and Meta-analysis

Daniel Umpierre, MSc[1]

Paula A. B. Ribeiro, MSc[1]

Caroline K. Kramer, MD, ScD [2]

Cristiane B. Leitão, MD, ScD [2]

Alessandra T.N. Zucatti, PED [2]

Mirela J. Azevedo, MD, ScD [2,4]

Jorge L. Gross, MD, ScD [2,4]

Jorge P. Ribeiro, MD, ScD [1,3,4]

Beatriz D. Schaan, MD, ScD [2,4*]

[1] Exercise Pathophysiology Research Laboratory, [2] Endocrinology Division, and [3] Cardiology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. [4] Department of Internal Medicine, Faculty of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

Abstract

Context Regular exercise improves glucose control in diabetes, but the association of different exercise training interventions on glucose control is unclear.

Objectives To conduct a systematic review and meta-analysis of randomized controlled clinical trials (RCTs) assessing associations of structured exercise training regimens (aerobic, resistance, or both) and physical activity advice with or without dietary cointervention on change in hemoglobin A1c (HbA1c) in type 2 diabetes patients.

Methods MEDLINE, Cochrane-CENTRAL, EMBASE, ClinicalTrials.gov, LILACS, and SPORTDiscus databases were searched from January 1980 through February 2011. RCTs of at least 12 weeks' duration that evaluated the ability of structured exercise training or physical activity advice to lower HbA1c levels as compared with a control group in patients with type 2 diabetes. Two independent reviewers extracted data and assessed quality of the included studies.

Results Of 4191 articles retrieved, 47 RCTs (8538 patients) were included. Pooled mean differences in HbA1c levels between intervention and control groups were calculated using a random-effects model. Overall, structured exercise training (23 studies) was associated with a decline in HbA1c level (−0.67%; 95% confidence interval [CI], −0.84% to −0.49%; *I2*, 91.3%) compared with control participants. In addition, structured aerobic exercise (−0.73%; 95% CI, −1.06% to −0.40%; *I2*, 92.8%), structured resistance training (−0.57%; 95% CI, −1.14% to −0.01%; *I2*, 92.5%), and both combined (−0.51%; 95% CI, −0.79% to −0.23%; *I2*, 67.5%) were each associated with declines in HbA1C levels compared with control participants. Structured exercise durations of more than 150 minutes per week were associated with HbA1c reductions of 0.89%, while structured exercise durations of 150 minutes or less per week were associated with HbA1C reductions of 0.36%. Overall, interventions of physical activity advice (24 studies) were associated with lower HbA1c levels (−0.43%; 95% CI, −0.59%

to −0.28%; *I2*, 62.9%) compared with control participants. Combined physical activity advice and dietary advice was associated with decreased HbA1c (−0.58%; 95% CI, −0.74% to −0.43%; *I2*, 57.5%) as compared with control participants. Physical activity advice alone was not associated with HbA1c changes.

Conclusions Structured exercise training that consists of aerobic exercise, resistance training, or both combined is associated with HbA1c reduction in patients with type 2 diabetes. Structured exercise training of more than 150 minutes per week is associated with greater HbA1c declines than that of 150 minutes or less per week. Physical activity advice is associated with lower HbA1c, but only when combined with dietary advice.

Keywords: Exercise training, Aerobic exercise, Strength training, Type 2 diabetes mellitus.

Introduction

Exercise is a cornerstone of diabetes management, along with dietary and pharmacological interventions.[1,2] Current guidelines recommend that patients with type 2 diabetes should perform at least 150 minutes per week of moderate-intensity aerobic exercise and should perform resistance exercise 3 times per week.[1,2] Previous meta-analyses[3-6] demonstrated that structured exercise training including aerobic and resistance exercises reduces hemoglobin A1c (HbA1c) levels by approximately 0.6%. However, only 1 previous review separately analyzed associations of aerobic exercise, resistance training, and the combination of aerobic exercise and resistance training on change in HbA1c levels.[5] Since publication of this meta-analysis, 2 large randomized trials[7,8] were published that reported contradictory findings regarding the types of structured exercise associated with declines in HbA1c levels. Sigal et al[7] found that aerobic or resistance exercise training alone improved glycemic control but the effects were more pronounced with both combined. In contrast, Church et al[8] observed that only the combination, but not aerobic and resistance training alone, reduced HbA1c levels.

In contrast to structured exercise training, physical activity is defined as any bodily movement produced by skeletal muscle contractions resulting in increased energy expenditure.[9] Although structured exercise training may be available to a subset of patients with type 2 diabetes, physical activity advice is more feasible and should be offered to most patients with type 2 diabetes. However, meta-analyses have not been performed to determine whether physical activity advice is associated with similar declines in HbA1c as compared with those associated with structured exercise.

This study consists of a systematic review with meta-analysis of randomized controlled clinical trials (RCTs) on the associations of structured exercise training and physical activity advice, respectively, on changes in HbA1c levels in patients with type 2 diabetes. Structured exercise training is categorized according to whether it consists of aerobic exercise, resistance training, or a combination of both.

Search Strategy and Study Selection

We searched the following electronic databases covering the period from January 1980 through February 2011: MEDLINE (accessed by PubMed), Cochrane Central Register of Controlled Trials, EMBASE, ClinicalTrials.gov, SPORTdiscus, and LILACS. In addition, we searched the references of published studies manually. The initial search comprised the terms *exercise*, *diabetes mellitus*, *physical activity*, and related entry terms associated with a highsensitivity strategy for the search of RCTs,[10] and was not limited by language.

The complete search strategy used for the PubMed database is shown in eBox 1. Only eligible full texts in English, Portuguese, or Spanish were considered for review. This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11]

Eligibility Criteria

We included RCTs that compared any category of structured exercise training (aerobic, resistance, or a combination of both) or physical activity advice with a control group of patients with type 2 diabetes older than 18 years, that evaluated HbA1c as an outcome, and reported means or differences between means and respective dispersion values of HbA1c at baseline and after the intervention. Structured exercise training was defined as an intervention in which patients were engaged in planned, individualized, and

supervised exercise programs. Physical activity advice was defined as an intervention in which patients were partially or not engaged in supervised exercise training, but received formal instructions to exercise regularly with or without an individualized exercise prescription.

Eligible studies included only individuals able to exercise, with no clinical manifestations limiting physical activity. Exclusion criteria are as follows: (1) studies of patients with type 1 diabetes or gestational diabetes; (2) RCTs that did not provide information regarding the associations of the intervention with HbA1c in the experimental group, the control group, or both; (3) duplicate publications or substudies of included trials; and (4) studies with less than 12 weeks of follow-up.

Data Extraction

Titles and abstracts of retrieved articles were independently evaluated by 2 investigators (D.U. and P.A.B.R.). Reviewers were not blinded to authors, institutions, or manuscript journals. Abstracts that did not provide enough information regarding the inclusion and exclusion criteria were retrieved for fulltext evaluation. Reviewers independently evaluated full-text articles and determined study eligibility. Disagreements were solved by consensus and if disagreement persisted, by a third reviewer (B.D.S.). To avoid possible double counting of patients included in more than 1 report by the same authors or working groups, patient recruitment periods were evaluated and if necessary, authors were contacted for clarification. The corresponding author was contacted as needed to obtain data not included in the published report. Two reviewers (D.U. and P.A.B.R.) independently conducted data extraction. Disagreements were solved by consensus or by a third reviewer (B.D.S.). Adherence to protocols, dropout rates, and adverse events were also extracted.

Assessment of Risk of Bias

Risk of bias was evaluated according to the PRISMA recommendation.[12] Study quality assessment included adequate sequence generation, allocation concealment, blinding of outcomes assessors, use of intention-to-treat analysis, and description of losses and exclusions. Studies without clear descriptions of an adequate sequence generation or how the allocation list was concealed were considered not to have fulfilled these criteria. Quality assessment was independently performed by 2 unblinded reviewers (D.U. and P.A.B.R) and disagreements were solved by consensus or by a third reviewer (B.D.S). The agreement rate between reviewers was κ=0.96 for quality assessment.

Data Analyses

Absolute changes in HbA1c were reported as differences between arithmetic means before and after interventions. Data from intention-to-treat analyses were entered whenever available in included RCTs. Pooled-effect estimates were obtained by comparing the least squares mean percentage change from baseline to the end of the study for each group, and were expressed as the weighted mean difference between groups. Calculations were performed using a random-effects model. Four comparisons were made with each group being compared with a nointervention (control) group: structured aerobic exercise training, structured resistance exercise training, structured combined aerobic/resistance exercise training, and physical activity advice. An α value=.05 was considered statistically significant.

Statistical heterogeneity of the treatment effect among studies was assessed using Cochran *Q* test, a threshold *P* value of .1 was considered statistically significant, and the inconsistency I^2 test in which values greater than 50% were considered indicative of

high heterogeneity.[13] We explored heterogeneity between studies using 3 strategies. First, we reran the meta-analyses removing each study at a time to check if a particular study was explaining heterogeneity. Second, stepwise meta-regression analyses were carried out. Using univariate meta-regression models, we assessed clinical and methodological variables that influenced the association of exercise with HbA1c levels. Likewise, similar procedures were undertaken to analyze particular variables that could explain heterogeneity in the physical activity advice meta-analysis. Thereafter, based on univariate meta-regression analyses, we constructed 4 multivariate models including baseline HbA1c plus exercise frequency (defined as the number of exercise sessions per week [model 1]); baseline HbA1c plus total exercise time spent in the program (defined as the cumulative product of exercise frequency, session duration, and number of weeks of training [model 2]); baseline HbA1c plus a variable indicating total exercise time of 150 minutes or less per week or more than 150 minutes per week [model 3]); and baseline HbA1c plus exercise intensity plus total exercise time spent in the program (model 4). Model 4 included covariates that were not significant in univariate regression, but were included based on clinical judgment of their importance. We evaluated the goodness of fit of each model using the adjusted R^2, which denotes the proportion of between- study variation explained by the covariates.[14,15] Third, we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of the intervention based on pre-specified relevant clinical information and on meta-regression analyses. For the structured exercise training meta-analysis results, we used a cutoff of 150 minutes per week to stratify studies according to their weekly amounts of exercise. RCTs evaluating physical activity advice were grouped according to the presence vs absence of a simultaneous dietary recommendation.

Because some studies compared multiple exercise interventions with a single control group, we split this shared group into 2 or more groups with smaller sample sizes weighted in relation to different exercise interventions. This approach was applied in order to have reasonably independent comparisons and overcome a unit-of-analysis error for studies that could contribute to multiple and correlated comparisons, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*.[13] Imputation and/or transformation methods were used for few studies that showed results as confidence intervals (CIs) or interquartile ranges.[16] Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error.[17] Funnel plot asymmetry was evaluated by Begg and Egger tests, and a significant publication bias was considered if the *P* value was less than .10. The trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of results.[18,19] All analyses were conducted using Stata software version 11.0 (Stata Inc, College Station, Texas).

Results

Description of Studies

From 4191 potentially relevant citations retrieved from electronic databases and searches of reference lists, 47 RCTs (including 23 RCTs of structured exercise training and 24 RCTs of physical activity advice) met the inclusion criteria. A flow diagram of search and selection is shown in eFigure 1.

Included studies had a total of 8538 patients. Of these, 848 patients were included in studies of structured aerobic exercise training, 261 in structured resistance exercise studies, 404 in structured combined aerobic/resistance exercise training studies, and

7025 in physical activity advice studies. Characteristics of these studies are summarized in Table 1 and Table 2.

Fifteen studies of structured exercise reported data on adherence. Of these, 14 trials reported adherence rates of more than 75%. Dropout rates were less than 20% in all but 2 of the 21 studies that reported this measure (Table 1). Adherence rates were not reported for the physical activity studies because of lack of accuracy (ie, self-reported data and reliance on patient recall). Dropout rates were less than 20% for 19 of the 24 physical activity intervention studies (Table 2).

No major adverse effects were reported (eTable 1). Minor adverse events for the structured exercise interventions and physical activity interventions most commonly included cardiovascular disease events that were not related to the intervention and musculoskeletal injury or discomfort (eTable 1). One study of a physical activity intervention included a high rate of hypoglycemia. Of 47 RCTs, 30 studies did not report data on adverse events (eTable 1).

Quality (Risk of Bias) and Publication Bias Assessment

Among the included studies, 36% presented adequate sequence generation (17 of 47), 17% reported allocation concealment (8 of 47), 17% had blinded assessment of outcomes (8 of 47), 96% described losses to follow-up and exclusions (45 of 47), and 13% used the intention-to-treat principle for statistical analyses (6 of 47) (eTable 2 and eTable 3).

Contour-enhanced funnel plots and the Egger regression test suggested an asymmetry in the analysis of structured exercise training (P=.02). However, the trim-and-fill computation revealed that publication bias did not interfere with the interpretation of results (eFigure 2, panel A). Regarding physical activity advice studies, neither the

Egger regression test nor the trim-and-fill computation showed any publication bias (*P*>.10) (eFigure 2, panel B).

Association of Interventions With the Primary End Point (HbA1c) Structured Exercise Training: Aerobic, Resistance, or Both.

The overall association of any structured exercise vs control with absolute HbA1c reduction (23 studies; 1533 patients) was −0.67% (95% CI; −0.84% to −0.49%; I^2, 91.3%; *P* for heterogeneity, <.001) (Figure 1). Eighteen studies (848 patients) demonstrated that structured aerobic exercise training was associated with an absolute HbA1c reduction of 0.73% (95% CI, −1.06% to −0.40%; I^2, 92.8%; *P* for heterogeneity <.001) as compared with control. Four articles (261 patients) demonstrated that structured resistance exercise training was associated with a decline in absolute HbA1c of 0.57% (95% CI, −1.14% to −0.01%; I^2, 92.5%; *P* for heterogeneity <.001) as compared with control. Seven articles (404 patients) demonstrated that the combination of aerobic and resistance exercise were associated with an HbA1c reduction of 0.51% (95% CI, −0.79% to −0.23%; I^2, 67.5%; *P* for heterogeneity <.001) as compared with control participants. In univariate meta-regression, baseline HbA1c level, exercise frequency, total time spent in exercise during the study, and weekly exercise duration of more than 150 minutes per week or of 150 minutes or less per week partially explained heterogeneity between structured exercise training studies (eTable 4). These covariates also were significant in the multivariate meta-regression models (eTable 4). Structured exercise of more than 150 minutes per week (18 observations, 826 patients) was associated with an absolute HbA1c reduction of 0.89% (95% CI, −1.26% to −0.51%; I^2, 91.4%; *P* for heterogeneity<.001). Structured exercise of 150 minutes or less per week (12 observations, 687 patients) was associated with an absolute reduction of 0.36% of

HbA1c (95% CI, −0.50% to −0.23%; I^2, 78.6%; *P* for heterogeneity <.001) (eFigure 3). When studies were omitted individually from the meta-analysis to assess possible individual influences on results, heterogeneity and weighted mean differences were unchanged.

Physical Activity Advice.

Twenty-four articles comparing physical activity advice (3529 patients) vs control (3496 patients) demonstrated that physical activity advice was associated with a decline in HbA1c of 0.43% (95% CI, −0.59% to −0.28%; I^2, 62.9%; *P* for heterogeneity <.001) (Figure 2). Covariates used in univariate analysis did not explain heterogeneity (eTable 4). Similarly, a multivariate meta-regression using baseline HbA1c and dietary recommendation (model 1) as covariates did not explain the between studies variance (overall, *P*=.17). In sensitivity analyses, physical activity associated with dietary advice (12 studies, 6313 patients) was associated with a 0.58% absoluteHbA1c reduction (95% CI, −0.74% to −0.43%; I^2, 57.5%; *P* for heterogeneity=.007) as compared with control. Physical activity advice alone (14 studies, 712 patients) was not associated with HbA1c changes as compared with control (Figure2). When studies were individually omitted from the meta-analysis, heterogeneity and weighted mean differences were unchanged.

Discussion

Our results demonstrate that in patients with type 2 diabetes, structured aerobic, resistance, or combined exercise training is associated with a HbA1c decline of −0.67%. Our analyses also demonstrate that structured exercise duration of more than 150 minutes per week was associated with greater benefit (0.89% reduction in HbA1c) than structured exercise duration of 150 minutes or less per week (0.36% reduction in

HbA1c). Structured exercise training was associated with a more pronounced HbA1c reduction compared with physical activity advice. A recommendation to increase physical activity was beneficial (0.43% HbA1c reduction), but only if combined with dietary recommendations.

This systematic review and meta-analysis of RCTs demonstrates important findings regarding the prescription of structured exercise training. First, aerobic, resistance, and combined training are each associated with HbA1c decreases, and the magnitude of this reduction is similar across the 3 exercise modalities. Interestingly, the weighted mean difference of −0.67% in HbA1c levels favorably compares with the decline in HbA1c associated with the addition of noninsulin antidiabetic drugs to maximal metformin therapy.[65] Second, our findings demonstrate that structured exercise of more than 150 minutes per week is associated with greater declines in HbA1c than structured exercise of 150 minutes or less per week in patients with type 2 diabetes.

This finding is important because the current guideline-recommended exercise duration is at least 150 minutes per week.[1,2] Although high-intensity exercise has been previously shown to have an association with HbA1c reduction, 4 our findings did not demonstrate that more intensive exercise was associated with greater declines in HbA1c. It is important to mention that, due to a great variability in exercise intensity descriptions, we used an intensity rating as previously reported.[5] Baseline HbA1c was one of the variables explaining the heterogeneity between studies, which underscores the greater magnitude of intervention effects in HbA1c among individuals with baseline HbA1c levels of greater than 7%, when compared with those with baseline HbA1c levels of less than 7%.[7,8,66,67] To our knowledge, this is the first systematic review to assess the association between physical activity advice interventions and glycemic control. Our results showed that physical activity advice was associated with lesser declines in

HbA1c than the studies evaluating structured exercise training. These results are consistent with a recent RCT demonstrating that supervised aerobic and resistance exercise training were more efficacious than physical activity advice alone in achieving declines in HbA1c.[68]

This review demonstrates that physical activity advice is only associated with HbA1c reduction when accompanied by a dietary cointervention. This highlights the need for a combined recommendation of these lifestyle interventions. Despite the fact that diet alone could improve glycemic control, most RCTs in our meta-analysis that evaluated physical activity plus a dietary intervention included a control group of a dietary intervention. Because HbA1c reduction in type 2 diabetes is associated with improved insulin resistance, and both exercise training/physical activity and body weight reduction induced by low-calorie diets1 have distinct mechanisms to elicit these effects, it is expected that these interventions applied together would result in greater metabolic effects.[2,69] Therefore, patients with type 2 diabetes should receive dietary recommendations in combination with advice to increase physical activity. Taken together, these results provide important information for clinical practice.[1,2] This study has limitations. Data extraction was unblinded, which is a potential source of bias. Additionally, high heterogeneity was identified in the meta-analyses, especially in the structured exercise training meta-analysis. To address this, we have performed analyses to identify clinical (eg, baseline HbA1c) and methodological differences (eg, amounts of exercise) between studies. Finally, the general quality of the studies was low, reflecting increased risk of bias in some studies. This may have contributed to the heterogeneity of our analyses.

Conclusions

Structured exercise, consisting of aerobic training, resistance training, or a combination of aerobic and resistance exercise training for at least 12 weeks, is associated with improved glycemic control in type 2 diabetic patients. Structured weekly exercise of more than 150 minutes per week was associated with greater declines in HbA1c. Structured exercise training reduced HbA1c to a larger degree than physical activity advice. Physical activity advice is beneficial only if associated with dietary recommendations.

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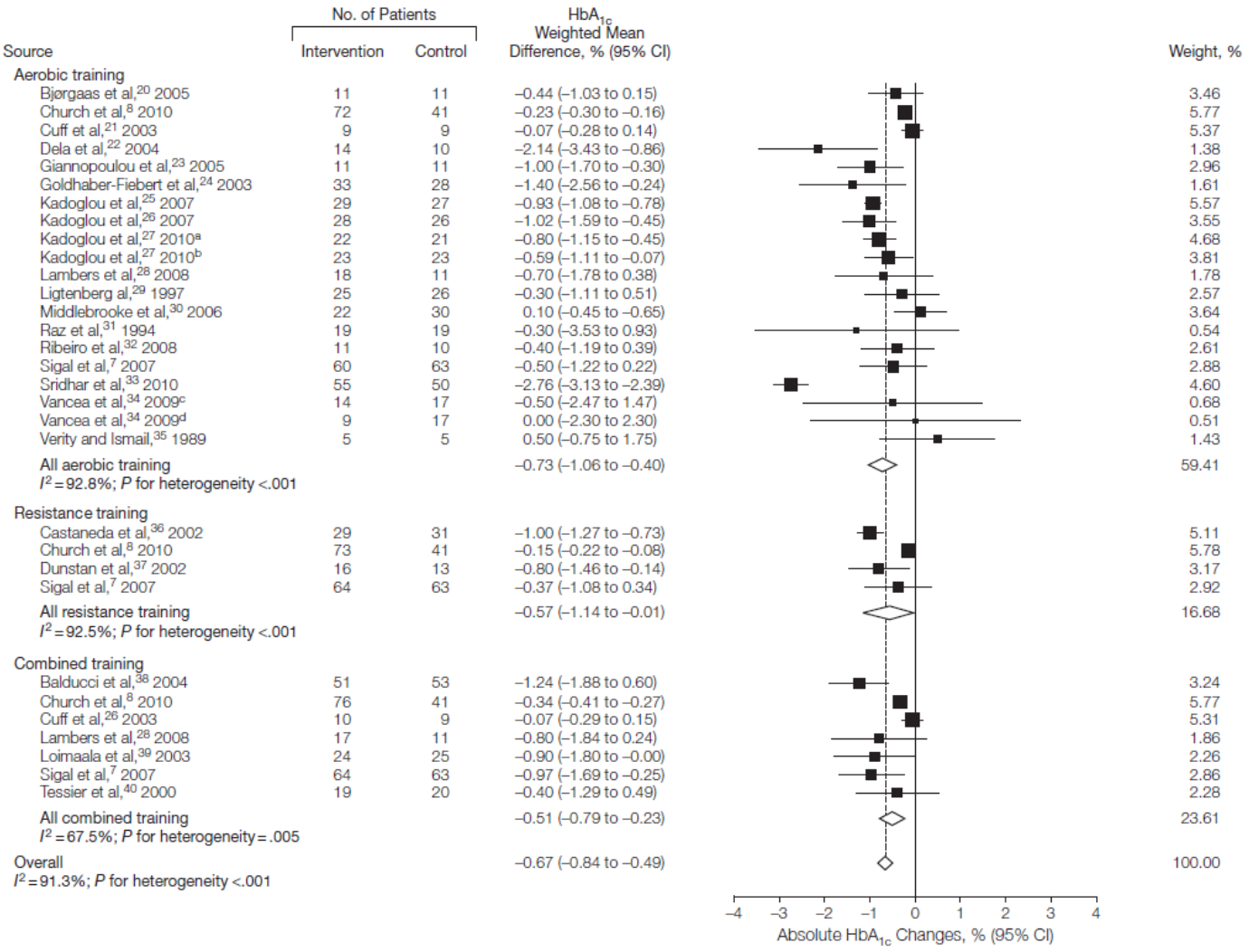
Figure 1. Absolute Changes in HbA_{1c} of Individual Studies of Structured Exercise Training vs No Intervention



CI indicates confidence interval. Changes in hemoglobin A_{1c} (HbA_{1c}) (absolute values) of individual studies included in the meta-analysis of structured exercise training (aerobic exercise, resistance training, and combined aerobic/resistance exercise) vs no intervention in patients with type 2 diabetes. Studies that included more than 1 modality or different training protocols within a same type of structured exercise training were evaluated as separate observations. Weights are from random-effects analysis.

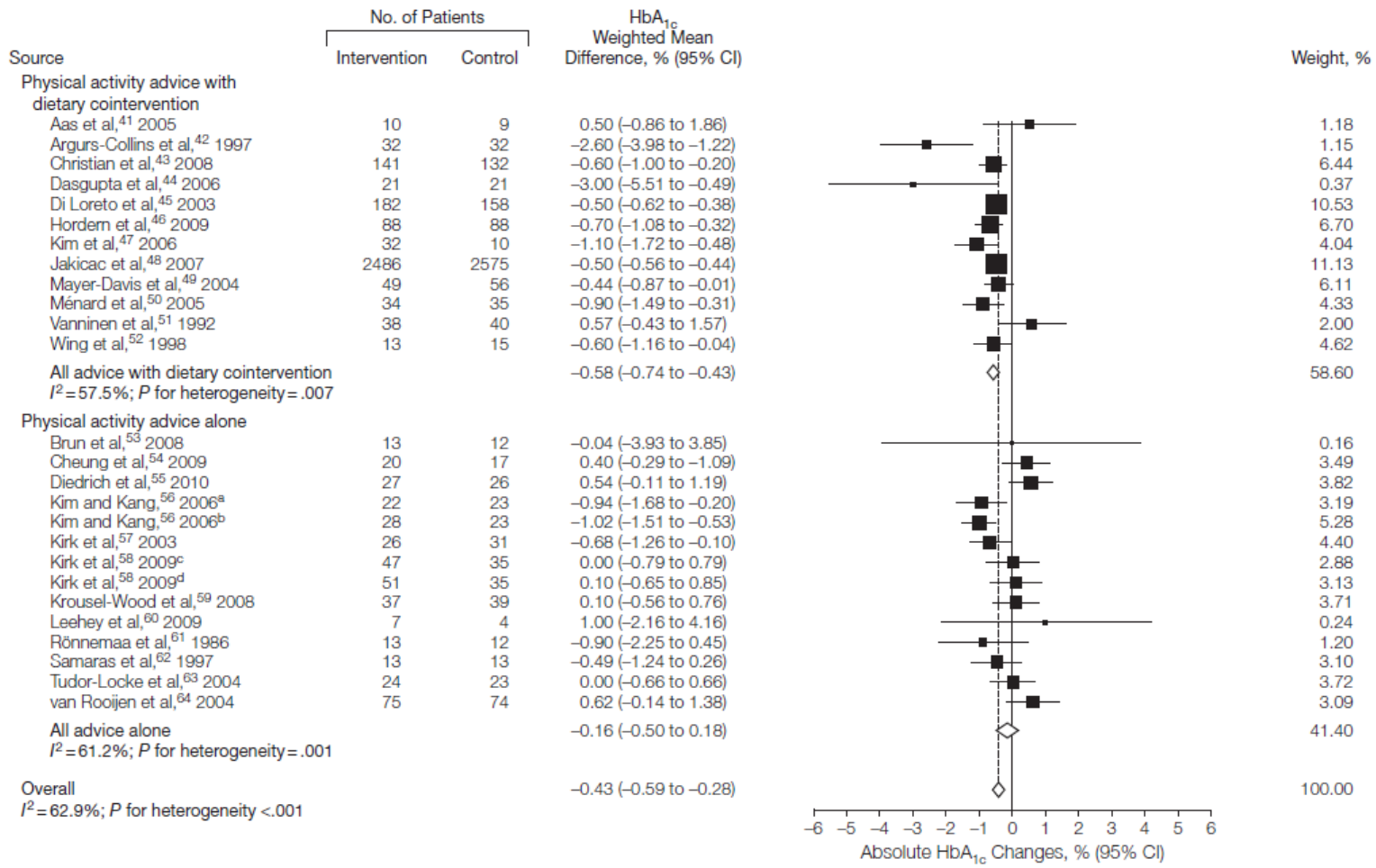
[a] Exercise and control subgroups.

[b] Exercise and control subgroups with rosiglitazone treatment as cointervention.

[c] Subgroup with exercise frequency of 3 sessions per week.

[d] Subgroup with exercise frequency of 5 sessions per week.

Figure 2. Absolute Changes in HbA_{1c} of Individual Studies of Physical Activity Advice vs No Intervention



CI indicates confidence interval. Changes in hemoglobin A_{1c} (HbA_{1c}) for individual studies included in the meta-analysis of physical activity advice vs no intervention in patients with type 2 diabetes according to the association or not of dietary intervention. Two studies provided more than 1 observation and were analyzed as distinct interventions to deliver physical activity. Weights are from random-effects analysis.

[a] Subgroup received advice in printed material.

[b] Subgroup received advice through a Web system.

[c] Subgroup received advice from an individual.

[d] Subgroup received advice in written form.

Table 1. Characteristics of the structured exercise studies included.

Study (Ref.)	Age mean (SD)	Intervention for the control group	Dietary co-intervention	Chronic comorbidities	Frequency (sessions/wk)	Session duration[a]	Program duration (weeks)	Adherence to exercise training (%)	Dropouts (%)
Aerobic training									
Bjorgaas et al.[20]	57 (8)	Diet advice care without exercise	Yes	Hypertension	2	90 min	12	77	20
Church et al [8]	54 (9)	Weekly stretching classes	No	Cardiovascular diseases Neuropathy Cancer	3	No fixed duration. Target of 150	~39	NR	Aerobic group: 4 Control group: 10
Cuff et al. [21]	59 (6)	Usual care	No	NR	3	75 min	16	92	0
Dela et al.[22]	52 (7)	Usual care	No	None	5	30-40 min	12	100	NR
Giannoupolou et al.[23]	58 (6)	Dietary planning without exercise	Yes	NR	3-4	60 min	14	NR	17
Goldhaber-Fiebert et al.[24]	59 (10)	Nutrition classes without exercise	Yes	Hypertension Dyslipidemia	3	60 min	12	NR	Aerobic group: 17.5 Control group: 20
Kadoglou et al.[25]	62 (5)	Usual care	No	Hypertension	4	30-45 min	26	92	Aerobic group: 3 Control group: 10
Kadoglou et al.[26]	59 (8)	Usual care	No	Hypertension	4	45-60 min	16	NR	Aerobic group: 6.5 Control group: 13
Kadoglou et al. [27]	59 (8)	One subgroup maintained habitual activities. Other subgroup received add-on RSG therapy.	No	NR	4	30-45 min	52	88	Aerobic group: 16 Control group: 12 Aerobic + RSG: 8 Control + RSG: 8
Lambers et al.[28]	52 (8)	Usual care	No	No major complications	3	50 min	12	≥ 85	Aerobic group: 5 Control group: 11
Ligtenberg et al.[29]	62 (5)	Educational program without exercise instructions	No	No major complications	3	50 min	12	97	Aerobic group: 17 Control group: 7

Middlebrooke et al.[30]	63 (8)	Usual care	No	Neuropathy Hypertension	3	30 min	26	99	Aerobic group: 24 Control group: 0
Raz et al.[31]	57 (7)	Lifestyle maintenance	No	Obesity Hypertension CAD PAD	3	45 min	12	68	Aerobic group: 5 Control group: 5
Ribeiro et al.[32]	55 (10)	Sedentary lifestyle	No	None	3	40 min	16	≥ 75	0
Sigal et al.[7]	54 (7)	Sedentary habitual lifestyle	No	Hypertension Depression	3	45 min	26	80	Aerobic group: 20 Control group: 5
Sridhar et al.[33]	61 (3)	Sedentary habitual lifestyle	No	Hypertension	5	30 min	52	NR	NR
Vancea et al.[34]	57 (6)	Counseling for spontaneous exercise	No	NR	3 or 5	30 min	20	NR	0
Verity and Ismail [36]	59 (4)	Lifestyle maintenance	No	Hypertension	3	60-90 min	16	NR	0
Resistance training									
Castaneda et al.[36]	66 (8)	Usual care	No	Cardiovascular disease Hypertension	3	~35 min, 5 exercises, 15 sets	16	90	Resistance group: 6 Control group: 0
Church et al [8]	57 (9)	Weekly stretching classes	No	Described above	3	9 exercises, 21 sets	~39	NR	Resistance group: 5 Control group: 10
Dunstan et al.[37]	67 (5)	Dietary intervention and stretching classes	Yes	Hypertension Arthritis Neuropathy Retinopathy	3	~45 min, 9 exercises, 27 sets	26	88	Resistance group: 16 Control group: 24
Sigal et al.[7]	55 (7)	Sedentary habitual lifestyle	No	Described above	3	7 exercises, 21 sets	26	85	Resistance group: 11 Control group: 5
Combined training									
Balducci et al.[38]	61 (9)	Lifestyle maintenance	No	Hypertension	3	60 min	52	> 90	Combined group: 18 Control group: 9

Church et al [8]	55 (8)	Weekly stretching classes	No	Described above	3	Not fixed time for aerobic; 9 sets of resistance exercises	~39	NR	Combined group: 5 Control group: 10
Cuff et al.[21]	63 (7)	Usual care	No	NR	3	75 min	16	92	0
Lambers et al.[28]	56 (10)	Usual care	No	No major complications	3	50 min	12	≥ 85	Combined group: 11 Control group: 11
Loimaala et al.[39]	53 (5)	Usual care	No	Hypertension	4	At least 30 min of aerobic; 24 sets of resistance exercises	52	NR	Combined group: 4 Control group: 0
Sigal et al.[7]	53 (7)	Sedentary habitual lifestyle	No	Described above	3	Both the aerobic and resistance	26	86	Combined group: 13 Control group: 5
Tessier et al.[40]	69 (5)	Lifestyle maintenance	No	NR	3	40	16	> 90	13

Abbreviations: RSG, Rosiglitazone; CAD, Coronary artery disease; PAD, Peripheral arterial disease. [a] Exercise characteristics do not include warm up and/or cool down periods. Age data represent weighted means and SDs between intervention and control groups. In studies with > 2 interventions, age data represent mean and SD of each intervention group.
NR indicates not reported.

Table 2. Characteristics of the physical activity advice studies included.

Study (Ref.)	Age mean (SD)	Intervention for the control group	Chronic comorbidities	Frequency (sessions/week)	Duration (weeks)	Weekly amount (min)	Pre-intervention	Dropouts (%)
Dietary co-intervention								
Aas et al.[41]	56 (NR)	Insulin treatment without lifestyle intervention	NR	2	52	120	No	PA group: 23 Control group: 25
Agurs-Collins et al. [42]	62 (6)	Usual care and information about nutrition	NR	3	26	90	No	PA group: 6 Control group: 12
Christian et al.[43]	53 (11)	Educational material about diabetes, diet and exercise	No major complications	NR	52	NR	No	PA group: 9 Control group: 13
Dasgupta et al.[44]	52 (NR)	Individualized dietary counseling	Cardiovascular disease	3	24	135	Yes	24
Di Loreto et al.[45]	62 (10)	Usual care, including dietary counseling	No major complications	NR	104	> 10 MET-h	No	PA group: 2 Control group: 0
Hordern et al [46]	56 (10)	Usual care	Myocardial dysfunction	NR	52	≥ 150	Yes	PA group: 21 Control group: 21
Kim et al.[47]	54 (9)	Basic dietary education	Hypertension	30	26	150	No	0
Look AHEAD Research Group [48]	59 (7)	Diabetes support and education	Hypertension Cardiovascular disease	5	52	175	Yes	PA group: 3 Control group: 4
Mayer Davis et al.[49]	61 (9)	Usual care	Hypertension	NR	52	150	Yes	19
Ménard et al.[50]	55 (8)	Usual care	Hypertension Dyslipidemia	3	52	45	Yes	PA group: 6 Control group: 3
Vanninen et al.[51]	53 (7)	Basic health education program	Hypertension CAD	3	52	158	Yes	0
Wing et al. [52]	56 (7)	Education about health habits and self-monitoring	No major complications	3	52	NR	Yes	0

No dietary co-intervention								
Brun et al.[53]	60 (10)	Repeated health evaluations	No major complications	2	52	75	Yes	0
Cheung et al.[54]	60 (8)	Lifestyle maintenance	NR	5	16	150	Yes	PA group: 5 Control group: 11
Diedrich et al.[55]	56 (12)	Education and self-management for diabetes	NR	NR	12	NR	Yes	PA group: 41 Control group: 38
Kim et al.[56]	55 (7)	Usual care and basic dietary education	Hypertension	3-5	12	90-150	No	0
Kirk et al.[57]	58 (8)	Usual care	Hypertension	5	26	150	No	PA group: 9 Control group: 11
Kirk et al.[58]	61 (10)	Usual care	NR	5	52	150	No	PA group: 9 Control group: 9
Krousel-Wood et al.[59]	57 (10)	Self-management education and exercise encouragement	No major complications	5	12	150	No	PA group: 18 Control group: 20
Leehey et al [60]	66 (NR)	Usual care and diabetes education	Chronic kidney disease Obesity	3	24	≥ 120	Yes	PA group: 0 Control group: 33
Rönnemaa et al.[61]	53 (NR)	Usual care	Hypertension Retinopathy	5-7	16	225-315	No	PA group: 13 Control group: 20
Samaras et al.[62]	61 (8)	Usual care	NR	NR	26	NR	Yes	0
Tudor-Locke et al.[63]	53 (5)	Usual care	Hypertension Dyslipidemia Allergies	NR	16	NR	Yes	PA group: 20 Control group: 23
Van Rooijen et al.[64]	55 (NR)	Relaxation intervention	Hypertension Arthritis	5	12	225	No	Physical activity: 6 Control group: 4

Abbreviations: PA group, physical activity advice group; CAD, Coronary artery disease. Age data represent weighted means and SDs between intervention and control groups.
NR indicates not reported.

Suplemmentary material

eBox 1. Literature search strategy used for the pubmed database

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#1 "Diabetes Mellitus, Type 2"[Mesh] OR Ketosis-Resistant diabetes [title/abstract] OR Ketosis Resistant diabetes [title/abstract] OR Maturity-Onset diabetes [title/abstract] OR Maturity Onset diabetes [title/abstract] OR Non Insulin Dependent diabetes [title/abstract] OR Non-Insulin-Dependent diabetes [title/abstract] OR Type 2 Diabetes [title/abstract] OR stable Diabetes [title/abstract] OR Diabetes Mellitus Type II [title/abstract] OR Maturity-Onset Diabetes Mellitus [title/abstract] OR Maturity Onset Diabetes Mellitus [title/abstract] OR MODY [title/abstract] OR NIDDM [title/abstract] OR Adult-Onset Diabetes Mellitus [title/abstract] OR Diabetes Mellitus Noninsulin Dependent [title/abstract]
#2 "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Resistance Training"[Mesh] OR "Muscle Stretching Exercises"[Mesh])) OR "Exercise"[Mesh] OR Exercise Isometric [title/abstract] OR Exercise Aerobic [title/abstract] OR Aerobic Exercises [title/abstract] OR Aerobic Exercise [title/abstract] OR Pilates Exercise [title/abstract] OR Training Resistance [title/abstract] OR Strength Training [title/abstract] OR Weight Lifting [title/abstract] OR Strengthening Program [title/abstract] OR Weight Bearing [title/abstract] OR Exercises [title/abstract] OR Physical Exercise OR Physical Exercise [title/abstract] OR Physical Exercises [title/abstract] OR Isometric Exercises [title/abstract] OR Isometric Exercise [title/abstract] OR Warm Up Exercise [title/abstract] OR Aerobic Exercises [title/abstract] OR Aerobic Exercise [title/abstract] Exercise Therapies [title/abstract] OR Pilates Training [title/abstract] OR Strength Training [title/abstract] OR Strengthening Programs [title/abstract] OR Weight Lifting Exercise Program [title/abstract] OR Weight Bearing Strengthening Program [title/abstract] OR Weight Bearing Exercise Program [title/abstract]
#3 "randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])
#4 #1 AND #2 AND #3

eTable 2. Adverse events reported in studies evaluating structured exercise training, and physical exercise advice

Study [Ref.]	Adverse events
Structured exercise training studies	
Bjorgaas et al [26]	Not available
Church et al [8]	21 events (Control: 3; Aerobic: 6; Resistance: 8 Combined: 4) Events: diverticulitis, emergency hysterectomy, lung cancer, 5 cardiovascular disease events (unrelated to intervention), blood clot.
Cuff et al [27]	Not available
Dela et al [28]	Not available
Giannopoulou et al [29]	Overall 5 (15%)
Goldhaber-Fiebert et al [30]	Not available
Kadoglou et al [31]	None
Kadoglou et al [32]	Not available
Kadoglou et al [33]	None
Lambers et al [34]	None
Ligtenberg et al [35]	50% experienced a single hypoglycemic episode. 1 case of progressive back pain; 1 case of vascular problem.
Middlebrooke et al [36]	None
Raz et al [37]	Not available
Ribeiro et al [38]	Not available
Sigal et al [7]	Serious: 7% (aerobic group) 1 case of newly diagnosed spinal stenosis 1 case of worsening angina Any injury or musculoskeletal discomfort: Aerobic: 27% ; Resistance: 28% ; Combined: 23% ; Control: 14%
Sridhar et al [39]	Not available
Vancea et al [40]	Not available
Verity and Ismail [41]	Not available
Dunstan et al [43]	Transient musculoskeletal soreness No major complications or injuries
Castaneda et al [42]	No injuries. Five hypoglicemic events 3 cases of chest pain (10%)
Balducci et al [44]	None
Loimaala et al [45]	Not available
Tessier et al [46]	Not available
Physical activity advice studies	
Aas et al [47]	3 nonspecified illness - 8% 1 tendon injury - 3%
Argus-Collins et al [48]	Not available
Brun et al [59]	Not available
Cheung et al [60]	Not available
Christian et al [49]	Not available
Dasgupta et al [50]	Acute coronary syndrome: 2% - Experimental group, but not attributed to the study intervention
Di Loreto et al [51]	Not available
Diedrich et al [61]	Not available
Hordern et al [52]	Not available
Kim et al [53]	Not available
Kim and Kang [62]	Not available
Kirk et al [63]	Not available
Kirk et al [64]	Not available
Krousel-Wood et al [65]	Non-cardiac chest pain, non-ischemic cardiomyopathy, shoulder pain (7 cases in control, 1 case in exercise group)
Leehey et al [66]	Not available
Look-Ahead et al [54]	Not available

Mayer Davis et al [55]	Not available
Ménard et al [56]	Hypoglycemia: 42% of the sample 2 cardiovascular events in each group
Ronemma et al [67]	Not available
Samaras et al [68]	Not available
Tudor Locke et al [69]	None
Van Rooijen et al [70]	Not available
Vanninen et al [57]	Not available
Wing et al [58]	Not available

eTable 3. Risk of Bias of Included Studies: Structured exercise training (n = 23)

	Adequate sequence generation	Allocation Concealment	Blinding of outcome	Description of losses and exclusions	Intention to treat analysis
Balducci et al.[40]	Unclear	Unclear	No	Yes	No
Bjorgaas et al.[22]	Yes	Yes	No	Yes	No
Castaneda et al.[38]	Unclear	Unclear	Yes	Yes	No
Church et al.[9]	Yes	Unclear	Yes	Yes	Yes
Cuff et al.[23]	Unclear	Unclear	Unclear	Yes	No
Dela et al.[24]	Yes	Unclear	No	No	No
Dunstan et al.[39]	Unclear	Unclear	No	Yes	No
Giannopoulou et al.[25]	Unclear	Unclear	No	Yes	No
Goldhaber-Fiebert et al.[26]	Yes	Unclear	Yes	Yes	No
Kadoglou et al.[27]	Unclear	Unclear	No	Yes	No
Kadoglou et al.[28]	Unclear	Unclear	No	Yes	No
Kadoglou et al. [29]	Yes	Yes	No	Yes	No
Lambers et al.[30]	Yes	Yes	Yes	Yes	No
Ligtenberg et al.[31]	Unclear	Unclear	No	Yes	No
Loimaala et al.[41]	Unclear	Unclear	No	Yes	No
Middlebrooke et al.[32]	Yes	U nclear	No	Yes	No
Raz et al.	Unclear	Unclear	No	Yes	No
Ribeiro et al.[34]	Unclear	Unclear	No	Yes	No
Sigal et al.[8]	Yes	Yes	Yes	Yes	Yes
Sridhar et al.[35]	Unclear	Unclear	No	Yes	No
Tessier et al.[42]	Unclear	Unclear	No	Yes	No
Vancea et al.[36]	Unclear	Unclear	No	Yes	No
Verity and Ismail[37]	Unclear	Unclear	No	Yes	No

eTable 4. Risk of Bias of Included Studies: Physical activity advice (n = 24)

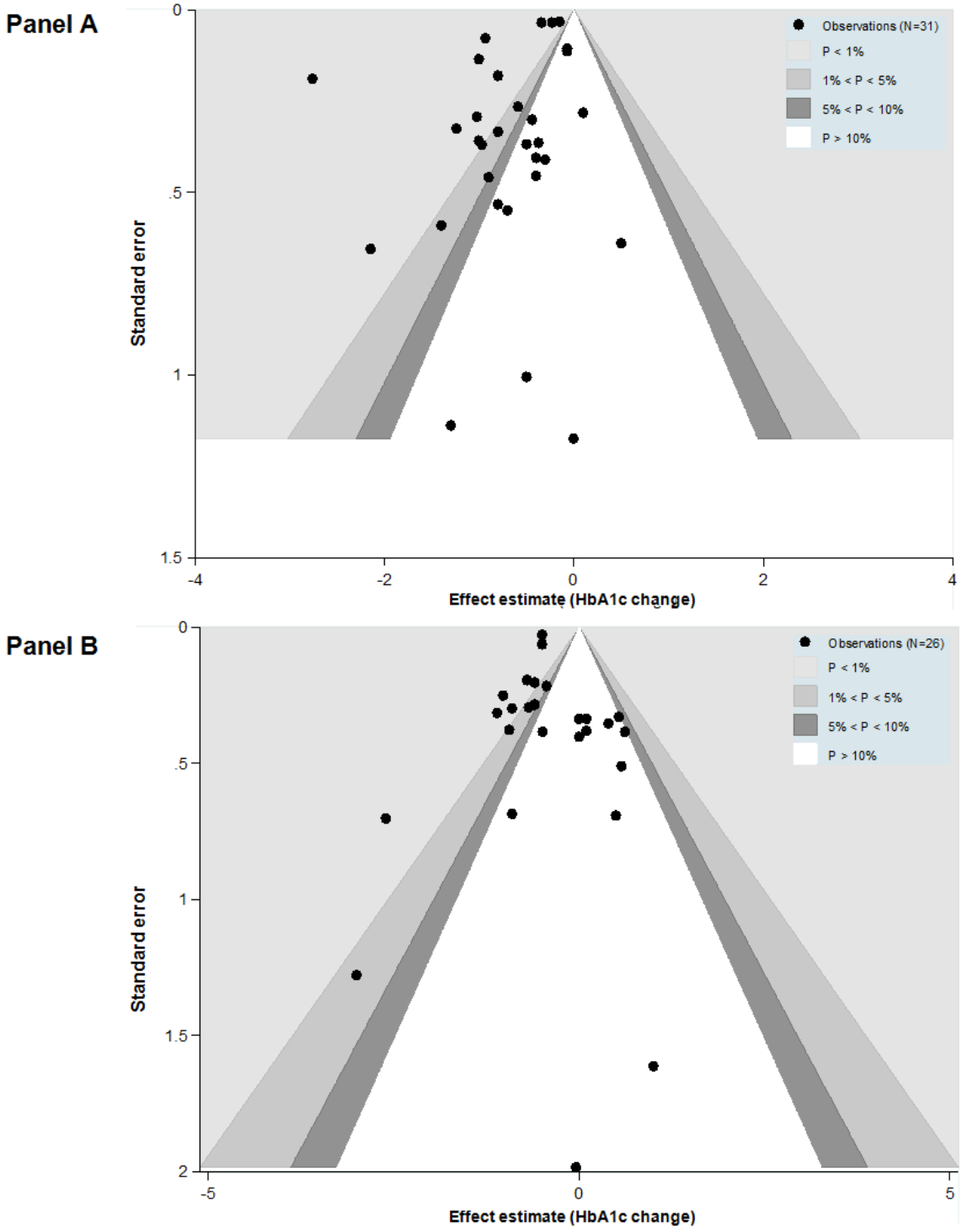
	Adequate sequence generation	Allocation Concealment	Blinding of outcome	Description of losses and exclusions	Intention to treat analysis
Aas et al.[43]	Unclear	Unclear	No	Yes	No
Agurs-Collins et al.[44]	Unclear	Unclear	Unclear	Yes	No
Brun et al.[55]	Yes	Unclear	No	Yes	No
Cheung et al.[56]	Unclear	Unclear	No	Yes	No
Christian et al.[45]	Yes	Yes	No	Yes	Yes
Dasgupta et al.[46]	Unclear	Unclear	Unclear	Yes	No
Di Loreto et al.[47]	Unclear	Unclear	No	Yes	Yes
Diedrich et al.[57]	Unclear	Unclear	Unclear	Yes	No
Hordern et al.[48]	Yes	Yes	Unclear	Yes	No
Kim and Kang.[49]	Unclear	Unclear	No	Yes	No
Kim and Kang.[58]	Unclear	Unclear	No	Yes	No
Kirk et al. [60]	Yes	Unclear	Yes	Yes	Yes
Kirk et al. [59]	Yes	Unclear	No	Yes	No
Krousel-Wood et al.[61]	Unclear	Unclear	Unclear	Yes	Yes
Leehey et al.[62]	Yes	Unclear	No	Yes	No
Look AHEAD Research Group[50]	Yes	Unclear	Yes	Yes	No
Mayer-Davis et al.[51]	Unclear	Unclear	Unclear	Yes	No
Ménard et al.[52]	Yes	Yes	No	Yes	No
Rönnemaa et al.[63]	Unclear	Unclear	No	Yes	No
Samaras et al.[64]	Unclear	Unclear	No	Yes	No
Tudor-Locke et al.[65]	Unclear	Unclear	No	Yes	No
Van Rooijen et al.[66]	Yes	Yes	Yes	Yes	No
Vanninen et al.[53]	Unclear	Unclear	No	Unclear	No
Wing et al.[54]	Unclear	Unclear	No	Yes	No

eTable5. Structured exercise training and physical activity advice in patients with type 2 diabetes: univariate and multivariate meta-regression models

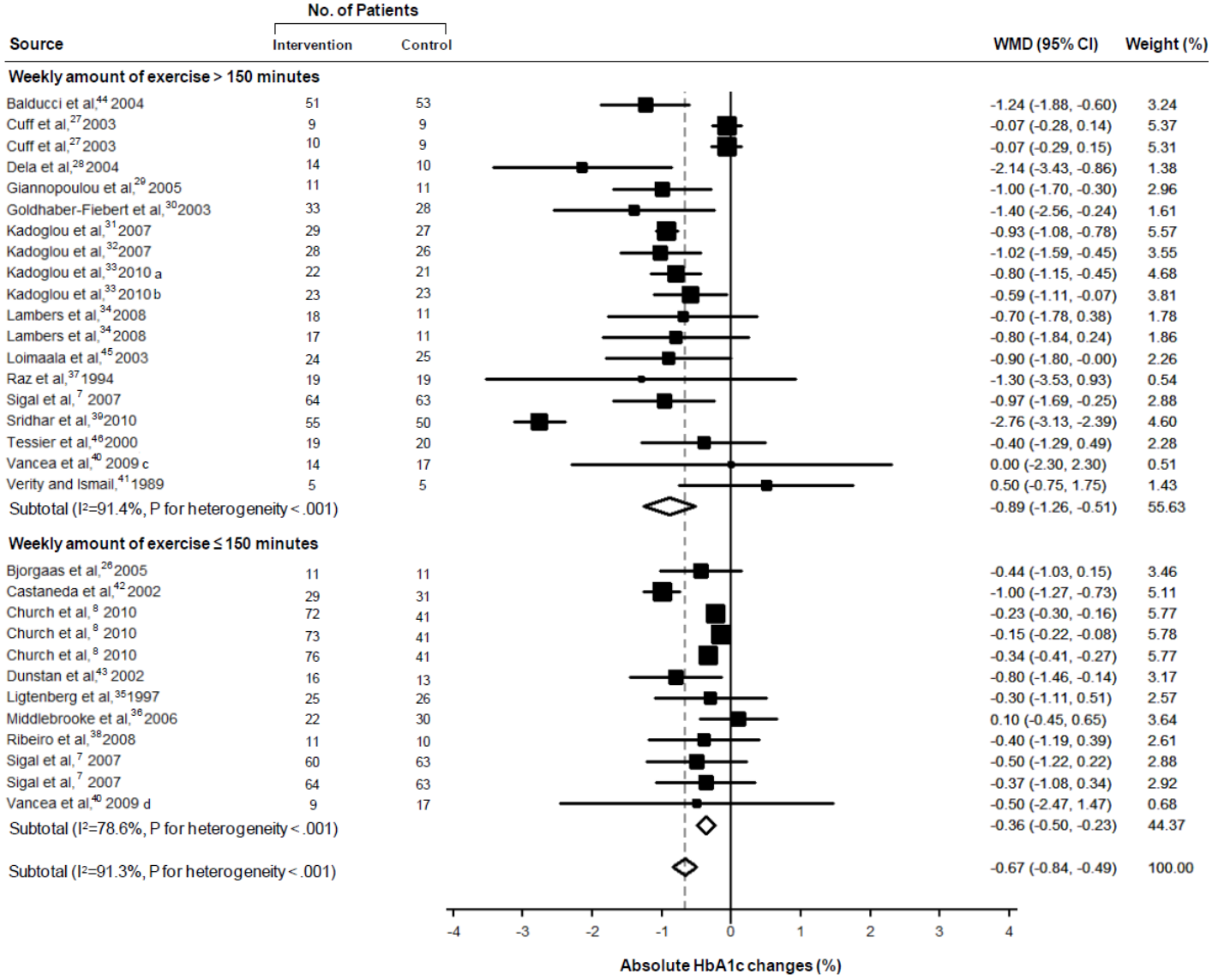
Structured exercise training				
Covariates	**Coefficient**	**95%CI**	**P**	**Adjusted R^2**
		Univariate analysis		
Baseline HbA1c	-0.37	-0.64 to -0.11	0.007	30.8
Weight change	0.006	-0.157 to 0.170	0.93	-6.84
BMI change	0.278	-0.100 to 0.657	0.141	18.20
Dietary co-intervention	-0.375	-1.253 to 0.503	0.390	-1.23
Adherence	0.016	-0.020 to 0.531	0.367	0.24
Frequency (sessions/wk)	-0.67	-0.96 to -0.38	<0.001	56.1
Total exercise time (h)	-0.005	-0.01 to -0.001	0.018	23.2
Amount equal/lower or higher than 150 min/wk	-0.48	-0.96 to -0.005	0.048	12.3
Exercise Intensity	0.26	-0.14 to 0.66	0.193	2.71
Program duration (wks)	-0.011	0.19 to -0.027	0.192	5.35
Session duration (min)	0.004	-0.012 to 0.022	0.57	-2.56
Weekly amount (min)	-0.005	-0.010 to 0.0003	0.065	11.05
Multivariate analysis				
Model 1: baseline HbA1c + exercise frequency			<0.001	69.6
Model 2: baseline HbA1c + Total exercise time			0.002	43.9
Model 3: baseline HbA1c + volume 150			0.002	46.5
Model 4: baseline HbA1c + intensity + frequency + session duration + total exercise time			<0.001	69.0
Physical activity advice				
Covariates	**Coefficient**	**95%CI**	**P**	**Adjusted R^2**
		Univariate analysis		
Baseline HbA1c	-0.118	-0.35 to 0.11	0.30	-4.65
Weight change	0.039	-0.14 to 0.22	0.63	-131.81
BMI change	-0.014	-0.33 to 0.31	0.93	-14.51
Dietary recommendation	-0.462	-0.95 to 0.03	0.06	24.70
Encouragement by phone	-0.053	-0.38 to 0.27	0.74	-8.32
Pre-intervention training	0.146	-0.41 to 0.70	0.59	-11.20
Study length	-0.001	-0.01 to 0.01	0.74	-9.36
Multivariate Model 1: baseline HbA1c + dietary co-intervention			0.175	14.3%

BMI, Body mass index; Total exercise time, total exercise time spent in the program (h).

eFigure2. Contour-enhanced funnel plot of each trial observation(s) effect size against the standard error



eFigure 3. Absolute changes in HbA1c of individual studies –Structured exercise training *vs*. No intervention (control) , according to weekly amount of exercise



ARTIGO II

Volume of Supervised Exercise Training Impacts Glycemic Control in Patients with Type 2 Diabetes

A Systematic Review with Meta-Regression Analysis

Volume de Treinamento Físico Supervisionado Impacta no Controle Glicêmico de Pacientes com Diabetes Tipo 2

Revisão Sistemática com Análise de Meta-Regressão

Volume of Supervised Exercise Training Impacts Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review with Meta-Regression Analysis

D. Umpierre[1],

P.A.B. Ribeiro[1]

B.D. Schaan[2,4]

J.P. Ribeiro[1,3,4]

[1] Exercise Pathophysiology Research Laboratory, [2] Endocrinology Division, and

[3] Cardiology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

[4] Department of Internal Medicine, Faculty of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

Corresponding author: Daniel Umpierre, ScD

Exercise Pathophysiology Research Laboratory

Rua Ramiro Barcelos 2350, Centro de Pesquisa Clínica – LaFiex, 3º andar

90035-003 Porto Alegre, RS

Phone: +55 51 9991-9192

Fax: +55 51 3359-8344

E-mail: daniel.umpierre@gmail.com

Abstract

Context: Supervised exercise programs improve glycemic control in type 2 diabetes, but training characteristics associated with reduction in HbA_{1c} remain unclear.

Objectives: We conducted a systematic review with meta-regression analysis of randomized clinical trials (RCTs) assessing the association between intensity and volume of exercise training (aerobic, resistance or combined) and HbA_{1c} changes in patients with type 2 diabetes.

Methods: Five electronic databases were searched (1980-2012) to retrieve RCTs of at least 12 weeks consisting of supervised exercise training *vs.* no intervention that reported HbA_{1c} changes and exercise characteristics. Two independent reviewers conducted study selection and data extraction.

Results: Twenty-six RCTs (2,253 patients) met the inclusion criteria. In multivariate analysis, baseline HbA_{1c} and exercise frequency explained nearly 58% of between-studies variance. Baseline HbA_{1c} was inversely correlated with HbA_{1c} reductions after the three types of exercise training. In aerobic training, exercise volume (represented by frequency of sessions) was associated with changes in HbA_{1c} (weighted r=-0.64), while no variables were correlated with glycemic control induced by resistance training. In combined training, weekly volume of resistance exercise explained heterogeneity in multivariate analysis and was associated with changes in HbA_{1c} levels (weighted r=-0.70).

Conclusions: Reduction in HbA_{1c} is associated with exercise frequency in supervised aerobic training, and with weekly volume of resistance exercise in supervised combined training. Therefore, exercise volume is a major determinant of glycemic control in patients with type 2 diabetes.

Keywords: Aerobic exercise, Resistance training, Type 2 diabetes mellitus, Glycosilated hemoglobin A

Introduction

Different exercise interventions determine benefits on glycaemic control in patients with type 2 diabetes.[1,2] Systematic reviews have consistently shown that supervised exercise training is associated with HbA_{1c} absolute reduction by approximately 0.6%.[2-5] Supervised aerobic, resistance or combined aerobic/resistance training are associated with greater decreases in HbA_{1c} than less strict strategies, such as exercise counseling alone.[2,6,7] Although important contributions have been made to the knowledge on the different types of exercise training for patients with type 2 diabetes,[8,9] key characteristics of volume and intensity in structured exercise prescriptions are inconclusive concerning their chronic impact on glycaemic control.

Since the manipulation of exercise training variables may optimize chronic glucose-lowering effects in different populations,[10,11] it would be useful to know which characteristics (e.g., frequency, duration of each session, total weekly duration, intensity) could be associated with larger benefits in patients with type 2 diabetes. A recent sub-analysis from the multicenter Italian Diabetes Exercise Study has shown that weekly exercise volume was positively related to improvements in quality of life in patients with type 2 diabetes,[12] which would probably facilitate the exercise adherence in a long-term perspective.[13] Supporting the importance of exercise volume, we have found that structured exercise durations of more than 150 min/week are associated with greater HbA_{1c} reductions in type 2 diabetes,[2] although previous data from aerobic training studies have indicated that exercise intensity, but not volume, was associated with reduction in HbA_{1c} levels.[3] Nonetheless, a 6-month trial has indicated that obese patients with type 2 diabetes present similar HbA_{1c} lowering after aerobic training of either low-to-moderate or moderate-to-high intensities.[14] Furthermore, exercise volume and intensity in resistance training or combined aerobic/resistance programs have not been studied so far.

Accordingly, this study consists of a systematic review with meta-regression analysis of randomized clinical trials (RCTs) on the associations of characteristics of supervised exercise training on changes in HbA_{1c} levels in patients with type 2 diabetes. Supervised exercise training is

categorized according to whether it consists of aerobic exercise, resistance training or a combination of both.

Methods

Search Strategy and Eligibility Criteria

We conducted a structured literature search for studies published from 1980 to June 2012. Electronic databases including MEDLINE (accessed by PubMed), Cochrane Central Register of Controlled Trials, EMBASE, SPORTdiscus and LILACS were searched. We also examined review articles and related references to identify other eligible studies. Initially, searches included terms such as "exercise", "diabetes mellitus", and "physical activity". The advanced search strategy used in the PubMed database is published elsewhere.[2] Only eligible studies published in English, Portuguese or Spanish were included. A total of 8 studies were excluded by language, (eFigure1). This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15]

Included RCTs were required to have at least one arm of supervised exercise training (aerobic, resistance, and/or a combination of both) compared with a control group of patients over 18 years old, with type 2 diabetes, that evaluated HbA_{1c} as an outcome and reported means or differences between means and statistical dispersion values of HbA_{1c}. Since the present review was designed to address characteristics of exercise training, we only included trials with structured and supervised exercise programs which are more likely to have strict control of the variables of interest, such as intensity, session duration, and frequency. We excluded studies that had nonhuman data, follow-up shorter than 12 weeks, which included patients with type 1 diabetes or gestational diabetes, and duplicate publications or sub-studies of included trials.

Two reviewers (D.U. and P.R.) independently assessed trials for inclusion in the systematic review. Disagreements were resolved by consensus or by a third reviewer (B.D.S). Corresponding

authors of potentially eligible studies were contacted as needed whenever their articles were suggestive of reporting duplicate data or part of the required information was missing in the published material.

Methodological quality of the included studies was evaluated by the independent reviewers, according to the PRISMA recommendation.[16] Assessment included adequate sequence generation, allocation concealment, blinding of outcomes assessors, use of intention-to-treat analysis, and description of losses and exclusions. Studies without clear descriptions of an adequate sequence generation or how the allocation list was concealed were considered not to have fulfilled these criteria.

Data Extraction

In order to generate weighted mean differences, HbA_{1c} absolute changes as well as standard deviations from all studies were extracted. Whenever standard deviation or standard error of the mean were no available, dispersion values were entered in the analysis by imputation methods.

Pertinent data regarding the methodological details of the studies, population characteristics, exercise training prescriptions, and outcomes were extracted in standardized forms by the independent reviewers. The frequency of exercise (sessions/week) and total time spent in exercise throughout the study, which are variables related to the training volume, were abstracted identically for the three types of supervised exercise training. In aerobic training interventions, we also extracted the session duration, weekly exercise volume and relative exercise intensity (based on percentages of maximum heart rate) of each study. We used established equations to derive aerobic training intensities expressed as percentages of the peak oxygen uptake (VO_2peak).[17] In resistance training interventions, we extracted the number of sets and repetitions, therefore calculating their weekly correspondents through the exercise frequency in each study. Resistance exercise intensities were computed as percentages of the one-repetition maximum (1-RM). In studies that used a range of repetitions to elicit maximal efforts at each set, the percent values of the submaximal weight loads

were obtained through an appropriate equation to the conversion from reps-to-fatigue to 1-RM.[18] In combined training studies, the characteristics of the aerobic and resistance components were extracted apart identically as described above for aerobic or resistance exercise training alone.

Statistical Analysis

Absolute changes in HbA_{1c} were treated as differences between arithmetic means before and after interventions. Thereafter, pooled weighted mean differences (WMD) were estimated by a random-effect model with the DerSimoniam-Laird method, and heterogeneity was assessed by Cochran Q and the I^2 statistic. Three comparisons were made with each supervised exercise training group being compared with a no intervention group, as follows: (1) aerobic exercise training *vs*. control; (2) resistance exercise training *vs*. controls; and (3) combined exercise training *vs*. control. Since the present systematic review was designed to analyze the characteristics of supervised exercise programs, we only used data from participants completing the follow-ups.

In order to explore which exercise characteristics of volume and intensity would be potentially associated with larger changes in HbA_{1c} levels, we initially ran meta-regressions by using the WMD estimates of HbA_{1c} and exercise training variables such as frequency of sessions, level of intensity, minutes of aerobic exercise per week, and sets of resistance exercise per week. Significant clinical and/or exercise variables in univariate models were also combined into multivariate meta-regression analyses. For each meta-regression model, adjusted r^2 indicated the proportion of between-study variance explained by the covariates.[19, 20] In addition, we generated correlations to test the association between HbA_{1c} WMDs with variables explaining heterogeneity in meta-regression analyses as well as with key exercise variables based on clinical judgment of their importance. All correlation analyses were weighted by the inverse of the variance of each observation, and scatter 'bubble' plots were constructed to graphically display the proportional weights of the different trials.

In trials in which multiple exercise interventions were compared with a single control group**,** we split this shared control group into two or more groups, with smaller sample sizes weighted in relation to each exercise group. Therefore, comparisons were reasonably independent and overcame a unit-of-analysis error for studies that could contribute to multiple and correlated comparisons.[21] All analyses were conducted using Stata 11.0 software (Stata, College Station, TX, USA).

Results

Systematic Review and Qualitative Assessment

After the exclusion of duplicate references, the search strategy resulted in 3,788 studies. Of these, 3,454 studies were excluded based on the titles and abstracts. Therefore, from 334 eligible articles that underwent full-text evaluation, 26 RCTs met the inclusion criteria and provided data on 2,253 patients. Of these, 935 patients were included in supervised aerobic exercise training, 249 in supervised resistance exercise training, and 1069 in supervised combined aerobic/resistance exercise training. The flow diagram of search and major reasons for exclusions is shown in eFigure 1 (supplementary material).

Characteristics of included studies are summarized in eTable 1 (supplementary material). Trials were published from 1989 to January 2012, and the majority were small studies with sample sizes ranging from 10 participants included in the smallest and 563 in the largest study. Mean duration of interventions was 25 weeks (range, 12 to 52). The 2,253 patients had mean age of 58 years (range, 53 to 69), mean baseline HbA_{1c} of 7.8 % (range, 6.3 to 12.5), and diabetes duration of 6 years (range, 2 to 10). In the quality assessment, 35% presented adequate sequence generation (9 of 26), 19% reported allocation concealment (5 of 26), 23% had blinded assessment of outcomes (6 of 23), 100% described losses to follow-up and exclusions (26 of 26), and 19% reported using the intention-to-treat principle for statistical analyses (5 of 26) (eTable 2).

Across 20 trials of aerobic exercise training, mean exercise frequency was 3 sessions per week, mean session duration was 48 minutes (not including warm-up and cool-down), and mean exercise intensity was 74% of the maximal heart rate (HR max). In 6 trials (33%), exercise intensity was transformed from submaximal rates of VO_2peak into their correspondent percentages of HRmax. All of the 5 trials using resistance exercise training had exercise frequency of 3 sessions per week. In these studies, number of total sets per session ranged from 14 to 27, and repetitions in each individual set ranged from 8 to 20. Regarding the weight loads used in each set, resistance exercise intensities ranged from 60% to 85% of the 1-RM. Across the 10 trials of combined exercise training, mean exercise frequency was 3 sessions per week (min-max: 2-4), mean session duration was 59 minutes (min-max: 45-90), mean aerobic exercise intensity was 73% of the HRmax (min-max: 60-85), whereas resistance exercise intensity in each set ranged from 40% to 85% of the 1-RM. We were unable to extract or derive exercise intensity in 7 interventions of aerobic training[23,25,26,34-36,38,41] and 3 interventions of combined training.[23,26,41] These studies were included in the systematic review, but their data were not entered in the analyses assessing exercise intensity as covariate.

Separate meta-analyses of studies with aerobic, resistance and/or combined exercise training were initially performed in order to generate effect sizes of each type of intervention. As expected, supervised exercise training was associated with improved glycaemic control, resulting in WMD of -0.70% (95% confidence interval [CI] -1.02, -0.38), -0.62 (95% CI -1.14, -0.11) and -0.47 (95% CI -0.64, -0.31) for aerobic, resistance, and combined exercise training, respectively.

Meta-Regression Analyses

Data from all trials indicated that baseline HbA_{1c}, exercise frequency and weekly exercise volume partly explained heterogeneity in studies (Table 1). In the multivariate analysis, baseline HbA_{1c} and weekly exercise volume explained nearly 58% of the variance between studies. As shown

in Figure 1, higher baseline levels of HbA_{1c} were associated with greater HbA_{1c} reductions after the three types of exercise training (weighted r=-0.52, P=0.001).

In supervised aerobic training, univariate analysis demonstrated that exercise frequency explained nearly 32% of the between-studies variance, which was also confirmed by a multivariate model including baseline HbA_{1c} and exercise frequency (Table 1). As depicted in Figure 2 (panel A), aerobic exercise frequency was associated with changes in HbA_{1c}, and showed a weighted regression slope of -0.39, indicating that, for each additional aerobic exercise session per week, there was a corresponding decline of 0.39% in HbA_{1c} levels (weighted r=-0.64, P<0.01). Interestingly, aerobic exercise intensity did not explain between-studies variance in the univariate analysis and showed no significant association with HbA_{1c} changes (P=0.3, Figure 2, panel B).

In trials of supervised resistance training, univariate meta-regression did not show any variables explaining heterogeneity between studies (Table 1), therefore limiting to enter volume or intensity variables in the multivariate analysis. Likewise, there were no correlations between weekly resistance exercise volume or resistance exercise intensity with changes in HbA_{1c} levels (Figure 3, panels A and B).

In trials of supervised combined training, volume and intensity were analyzed in relation to aerobic and resistance components separately. As shown in Table 1 and Figure 4, intensity of aerobic as well as of resistance exercises was not associated with changes in HbA_{1c}. Likewise, meta-regression and correlation analyses did not indicate association between aerobic exercise volume and HbA_{1c} changes induced by combined training. On the other hand, the weekly volume of resistance exercise in this type of training trended to significance in univariate analysis, and explained heterogeneity between studies when subsequently combined with baseline HbA_{1c} in the multivariate meta-regression (Table 1). Figure 4 (panel C) shows that resistance exercise volume was inversely correlated with weighted mean differences in HbA_{1c} levels (weighted r=-0.70, P=0.04), showing a weighted regression slope of -0.02, indicating that, for each additional resistance exercise set per

week, there was a corresponding decrease of 0.02% in HbA_{1c} levels after combined training interventions.

Discussion

The present systematic review provides an updated synthesis of the factors associated with improvements in glycaemic control induced by different types of supervised exercise training in type 2 diabetes. Overall, higher baseline HbA_{1c} levels are associated with greater reduction in HbA_{1c} levels after exercise interventions, supporting previous observations.[2,8,9] Although no exercise variables were found as possible candidates to explain the effects of resistance training, the volume of exercise was associated with HbA_{1c} reductions in supervised aerobic training as well as in combined aerobic/resistance training studies. More specifically, we found that each aerobic exercise session added within a week may impact on additional decline of 0.36% in HbA_{1c} levels. Interestingly, as we explored the aerobic and resistance components of combined training studies separately, the volume of resistance exercise was the characteristic associated with changes in HbA_{1c} levels in this training modality.

Through a sensitivity analysis published recently, we have observed that weekly exercise durations longer than 150 minutes are associated with absolute HbA_{1c} reductions of 0.89% in patients with type 2 diabetes.[2] Although this estimate was derived from a pooled analysis of studies with aerobic, resistance and combined exercise training, it highlighted an important role of the exercise volume in the exercise-induced glycaemic improvements. In this context, the present study demonstrates that the frequency of exercise is the specific factor more likely underlying the beneficial effects of aerobic training, meaning that the repetition of exercise sessions may be more important than longer or more intense sessions.

To our knowledge, only one previous systematic review with meta-analysis was designed to address quantitatively the characteristics of exercise training in type 2 diabetes.[3] In contrast with our

findings for supervised aerobic training, that previous study[3] showed that weekly volume was not associated with glycaemic control, whereas exercise intensity was inversely correlated with HbA_{1c} levels after aerobic training interventions. We would attribute such conflicting results to fundamental differences in most included studies, which reflect distinct eligibility criteria regarding the minimal duration of exercise training interventions, training group assignments (as in the aerobic arm of the analysis we entered groups performing aerobic exercise alone), and the number of studies analyzed (an inherent limitation to compare systematic reviews over time). Interestingly, a study has shown that 6 months of continuous aerobic training at low-to-moderate intensity or interval training at moderate-to-high intensities, matched for energy cost, induced similar HbA_{1c} reductions in patients with type 2 diabetes.[14] While a randomized trial[11] has indicated the importance of exercise volume for improvements in insulin sensitivity in non-diabetic individuals, other studies[22-24] demonstrate controversial results regarding the role of the intensity in aerobic programs. In accordance with the findings of the present analysis, we have recently shown that lower (55 ± 2 % of HRmax) and higher intensity (79 ± 3 % of HRmax) aerobic training resulted in similar reductions of HbA_{1c} in patients with type 2 diabetes or metabolic syndrome.[25] However, aerobic training at higher intensity resulted in larger improvement in endothelial function, indicating that more clinical trials should be conducted to better define the best training intensity for different outcomes.[25] Considering the inverse relationship between exercise volume and intensity, it is reasonable to think that the exercise intensity does not limit additional improvements in glycaemic control, but instead, the lower volume required to perform exercise at this level of effort. In this regard, a 10-week exercise training trial combining moderate cycling with episodes of very intense exercise has indicated important HbA_{1c} reductions in patients with type 2 diabetes.[26]

In resistance training programs, meta-regression models as well as weighted correlations did not show relationship between intensities and changes in HbA_{1c}. Although gains in lean body mass may have positive association with enhanced insulin action in different populations,[27-29] resistance

training seems to improve insulin sensitivity and reduce HbA_{1c} even without increases in muscle mass,[30] through increases in GLUT4 content and insulin signaling.[31] Therefore, exercise intensity would not necessarily need to induce muscle hypertrophy to improve glucose control. We point out that the exercise frequency was the same (3 sessions/week) in all resistance training studies, therefore limiting our analysis only on the association between HbA_{1c} and volume of resistance exercise. However, we also did not observe significant associations between the number of sets or repetitions with changes in HbA_{1c}, suggesting that training volume plays a minor role in glycaemic control for isolated resistance training.

Regarding the combined training studies, the novel finding of our study is that the volume of resistance exercises seems to be the differential characteristic related to glycaemic control, as reflected by the inverse association between the number of sets per week and HbA_{1c} levels. Given that the mean duration of the aerobic component in combined interventions was 33 minutes per session, we would expect larger HbA_{1c} reductions when more sets of resistance exercises are added to that amount of aerobic exercise. Supporting this notion, results from a RCT comparing aerobic, resistance and combined training also suggest the importance of the exercise volume in lowering HbA_{1c} after combined programs.[9] Although our analysis of the distinct aerobic and resistance components indicates that the resistance exercise volume most importantly underlies the benefits of combined training, it is still a matter of discussion whether this type of training could induce additional HbA_{1c} reductions when volume is comparable to aerobic or resistance training alone.[8,9,32,33] Considering the results shown, we speculate that there should be a minimal amount of aerobic exercise (~33 min) so that the effects of high-volume resistance exercise could be considerably elicited in combined exercise programs. Moreover, although the findings may seem counterintuitive, the resistance exercise in combined training is not comparable to the high-intensity of aerobic exercise. This result suggests that – once the volume is appropriate – the use of additional resistive exercises will also induce larger reductions in HbA_{1c} levels.

One strength of this study is that we performed a systematic review to quantitatively assess weighted estimates related to the characteristics related to the effects of supervised exercise training. It indicates reductions of approximately 0.6% in levels of HbA_{1c}, which is numerically comparable to the addition of noninsulin antidiabetic drugs to metformin therapy.[34] Further, it extends the knowledge for designing exercise prescriptions aiming to optimize glycaemic control in type 2 diabetes. By assessing several variables in aerobic training studies, we found the importance of frequency of sessions. Furthermore, we conducted separate analysis of combined training studies and added insight on the likely role of resistance exercises as part of combined aerobic/resistance training. Therefore, the present study demonstrates objective training factors which may be further investigated in randomized clinical trials as well as suggests the need to address such exercise training differences in future guidelines.

Since increased exercise intensity might reduce the compliance to supervised exercise programs,[35] our findings underscore the recommendation of more frequent exercise sessions for patients with type 2 diabetes.[1]

There are some limitations to our analysis. First, as a systematic review of published literature, we extracted information which is sometimes dynamic throughout the studies, such as progressive exercise durations and/or intensities. Therefore, results might have a potential bias due to averages which need to be generated in secondary data analysis. To minimize this effect, we contacted authors either to clarify methodological issues or to obtain additional data. When the information was considerably imprecise (e.g., exercise intensity in some studies), data were not entered in qualitative analyses. Second, we analyzed only supervised exercise interventions, which may not be feasible to all patients with type 2 diabetes. Thus, our findings are relevant to center-based exercise prescriptions, but cannot be generalized to all exercise programs in type 2 diabetes. We point out that, despite well-known health benefits, physical activity recommendation alone has not shown to be effective in improving glycaemic control,[2,6,7] which highlights the need of improved

strategies for these interventions. Finally, the present study suggest the need of a large multi-arm trial comparing different regimens of exercise training focusing either intensity or volume for patients with type 2 diabetes.

Reduction in HbA_{1c} is associated with exercise frequency in supervised aerobic training, and with weekly volume of resistance exercise in supervised combined training. Therefore, exercise volume is a major determinant of glycaemic control in patients with type 2 diabetes submitted to structured exercise programs.

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Contribution statement

DU, BDS and JPR conceived and designed the project. DU and PABR reviewed the retrieved studies and conducted data extraction. DU conducted data analyses. DU, PABR, BDS and JPR were responsible for data interpretation. DU drafted the manuscript, and BDS and JPR revised it critically for intellectual contributions. BDS and JPR coordinated the study development. All authors reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Duality of interest

JPR reports having received lecturing fees from AstraZeneca and Servier; and grant support from Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Servier, and Takeda. The other authors declare that there is no duality of interest associated with this manuscript.

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Figure 1

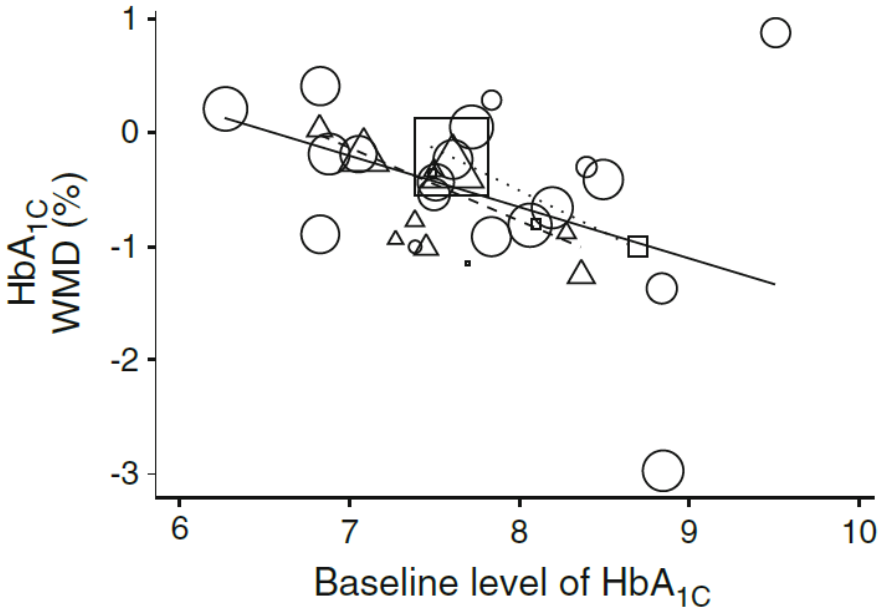


Fig. 1 Association between baseline levels of HbA1c and changes in HbA1c after different types of supervised exercise training. Each observation represents the WMD of HbA1c between the different interventions of exercise training and control groups. The size of the symbols is proportional to the inverse variance of each study in the pooled analysis. Meta-regression lines are specific for each type of intervention: continuous line, aerobic training studies; dotted line, resistance training studies; and dashed line, combined training studies.

Circles, supervised aerobic training; squares, supervised resistance training; triangles, supervised combined training. Slope for weighted regression, $y=-0.17x+0.60$. Weighted correlation, $r=-0.52$, $p<0.001$.

Note that HbA1c levels are shown in %. To convert values for HbA1c in % into mmol/mol, subtract 2.15 and multiply by 10.929.

Figure 2

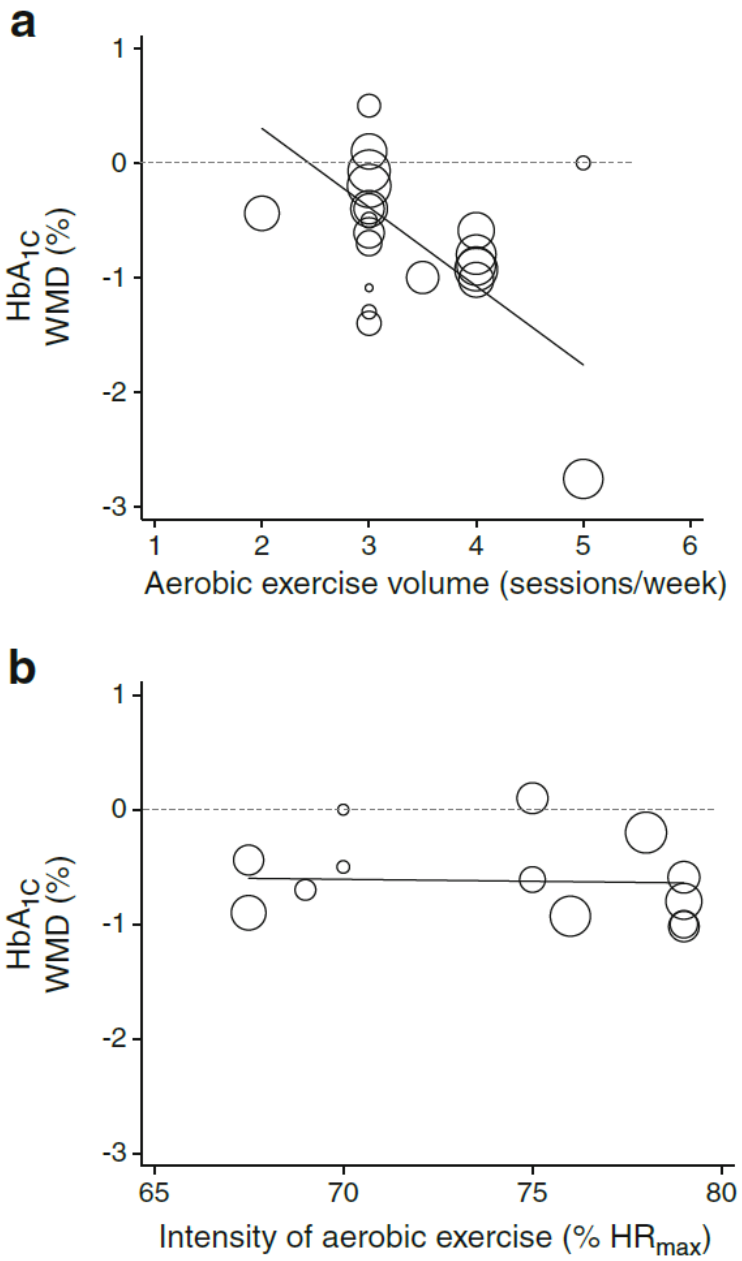


Fig. 2 Association between exercise volume (a) and intensity (b) with HbA1c changes in studies of supervised aerobic training. Exercise volume is expressed as the frequency of sessions within a week and intensity is expressed as submaximal percentages of the HRmax. Each observation represents the WMD of HbA1c between the aerobic training and control groups. The size of the circles is proportional to the inverse variance of each study in the pooled analysis. Slopes for weighted regressions, $y=-0.39x+0.65$ and $y=-0.03x+2.03$, for aerobic volume and intensity, respectively. Weighted correlations, $r=-0.64$, $p<0.002$ and $r=-0.32$, $p=0.3$ for aerobic volume and intensity, respectively.

Figure 3

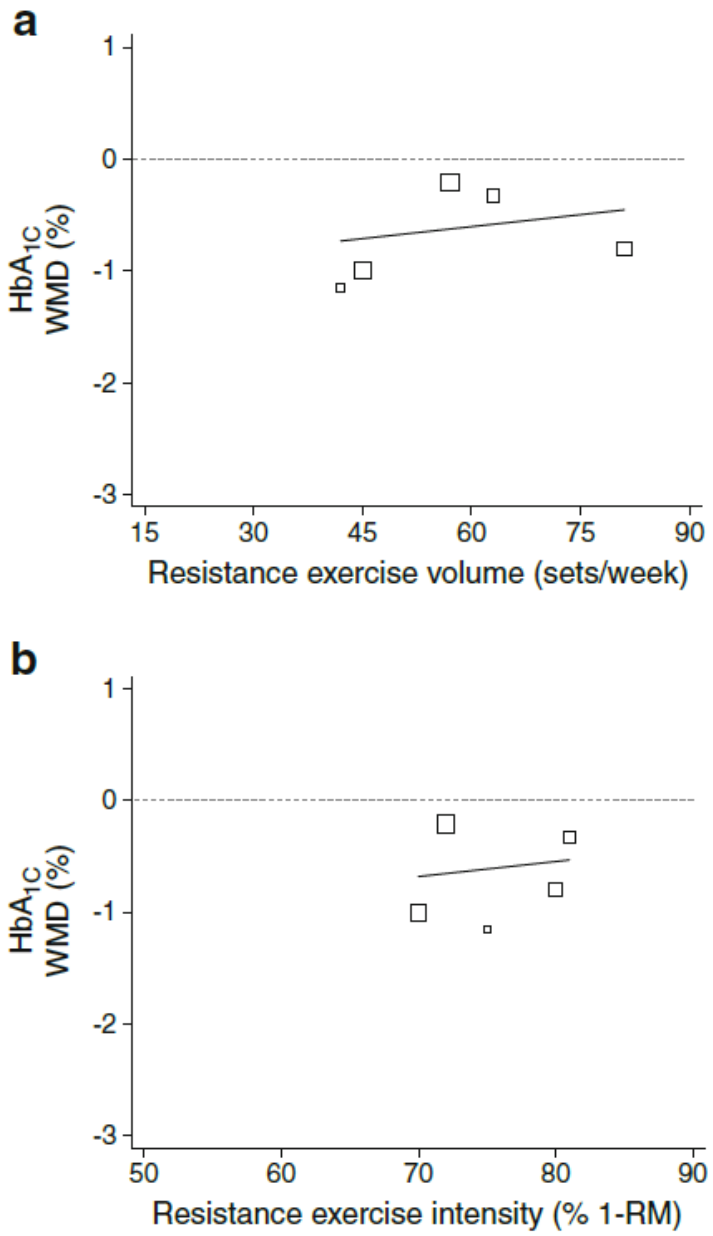


Fig. 3 Association between exercise volume (a) and intensity (b) with HbA1c changes in studies of supervised resistance training. Exercise volume is expressed as the number of sets within a week and intensity is expressed as submaximal percentages of the 1-RM. Each observation represents the WMD of HbA1c between the resistance training and control groups. The size of the squares is proportional to the inverse variance of each study in the pooled analysis. Slopes for weighted regressions, y=−0.01x−1.30 and y=−0.02−2.12 for resistance volume and intensity, respectively. Weighted correlations, r=0.26, p=0.7 and r=0.18, p=0.8 for resistance volume and intensity, respectively.

Figure 4

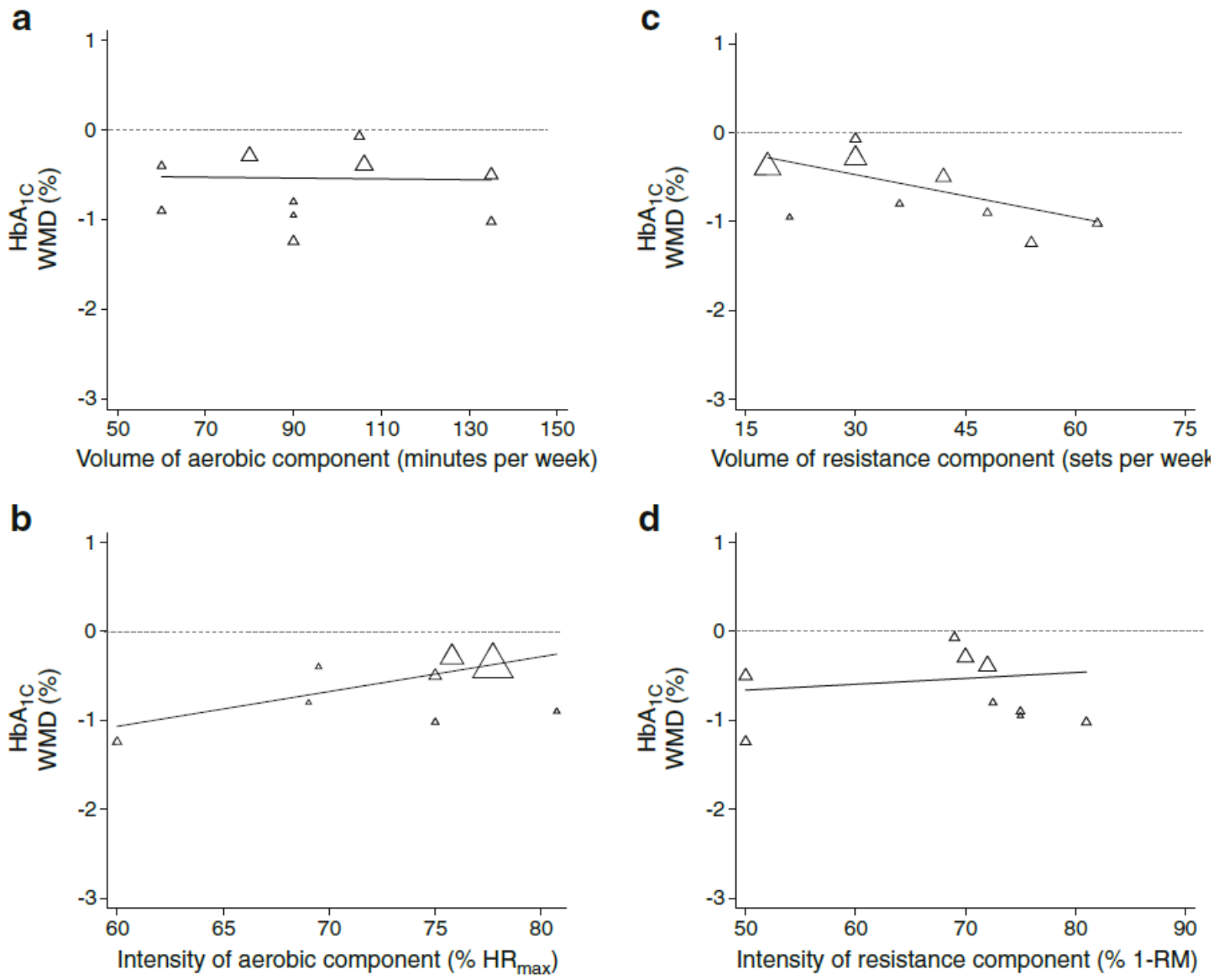
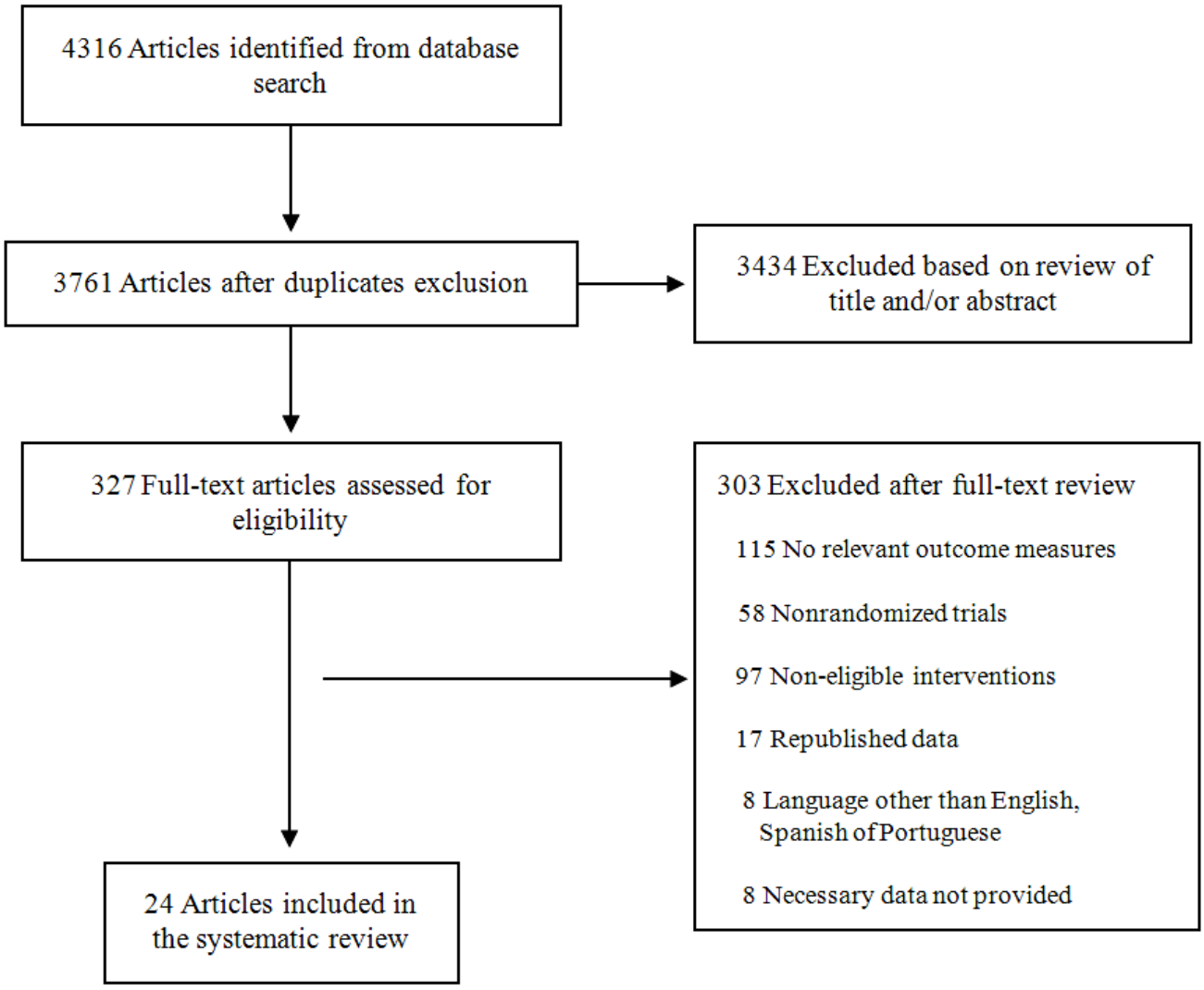


Fig. 4 Association between exercise volume and intensity with HbA1c changes in studies of supervised combined training showing the aerobic and resistance components separately. Scatterplots show both aerobic (a, b) and resistance (c, d) components. Exercise volume is expressed as minutes of aerobic exercise per week for the aerobic component or number of sets per week for the resistance component. Likewise, intensity is expressed as percentages of HRmax or 1-RM for aerobic and resistance components, respectively. Each observation represents the WMD of HbA1c between the combined training group and control group. The size of the triangles is proportional to the inverse variance of each study in the pooled analysis. Slopes for weighted regressions and weighted correlations were, respectively: $y=10^{-5}-05x-0.65$ and $r=-0.08$, p00.8 for the volume of aerobic component, and $y=0.02x-2.5$ and $r=0.67$, $p=0.07$ for the intensity of aerobic component. For the resistance components, slopes for weighted regressions and weighted correlations were, respectively: $y=-0.02x-0.10$ and $r=-0.70$, $p=0.04$ for the volume of the resistance component, and $y=0.001x-0.76$ and $r=0.27$, $p=0.5$ for the intensity of the resistance component.

Supplementary Material

eFigure 1: Flow diagram of selection of studies for inclusion and major reasons for exclusion



eTable 1: Characteristics of studies included in the systematic review.

Study (Ref.)	Age mean (SD)	Sample size (completers only)	Dietary cointervention	Frequency (sessions/week)	Aerobic [a] and/or Resistance volume	Program duration (weeks)	Intensity description	Adherence to exercise training (%)
Aerobic training								
Bjorgaas et al. [1]	57 (8)	AT: 11 (only men) CG: 11 (only men)	Yes	2	90 min	12	50 to 85% of maximum HR	77
Church et al [2] [b]	54 (9)	AT: 52 CG: 41	No	3	121 min [c]	~39	66% of the VO_2peak (averaged from the 3 last months of study)	NR
Cuff et al. [3]	59 (6)	AT: 9 (only women) CG: 9 (only women)	No	3	75 min	16	60 to 75% of HR reserve	92
Giannoupolou et al. [4]	58 (6)	AT: 11 (only women) CG: 11 (only women)	Yes	3-4	60 min	14	65 to 70% of VO_2peak	NR
Goldhaber-Fiebert et al. [5]	59 (10)	AT: 33 CG: 28	Yes	3	60 min	12	Brisk walking	NR
Jorge et al. [6]	54 (10)	AT: 12 CG: 12	No	3	60 min	36	Heart rate corresponding to the lactate threshold	97
Kadoglou et al. [7]	62 (5)	AT: 29 CG: 27	No	4	30-45 min	26	50 to 75% of VO_2peak	92

Kadoglou et al. [8]	59 (8)	AT: 28 CG: 26	No	4	45-60 min	16	50 to 85% of VO_2peak	NR
Kadoglou et al. [9]	59 (8)	AT: 45 CG: 44	No	4	30-45 min	52	50 to 80% of VO_2peak	88
Kadoglou et al. [10]	61 (5)	AT: 26 CG: 27	No	4	45 min	12	60 to 75% of maximum HR	85
Kurban [11]	54 (7)	AT: 30 CG: 30	No	3	30 min	12	NR	NR
Lambers et al. [12]	52 (8)	AT: 18 CG: 11	No	3	50 min	12	60 to 85% of HR reserve	≥ 85
Middlebrooke et al. [13]	63 (8)	AT: 22 CG: 30	No	3	30 min	26	70 to 80% of maximum HR	99
Raz et al. [14]	57 (7)	AT: 19 CG: 19	No	3	45 min	12	65% of the VO_2peak	68
Ribeiro et al. [15]	55 (10)	AT: 11 CG: 10	No	3	40 min	16	HR between the anaerobic threshold and respiratory	≥ 75
Sigal et al. [16] [b]	54 (7)	AT: 39 CG: 63	No	3	45 min	26	75% of maximum HR (performed during the 10 last weeks of intervention)	80
Sridhar et al. [17]	61 (3)	AT: 55 CG: 50	No	5	30 min	52	NR	NR
Vancea et al. [18]	57 (6)	AT: 23 CG: 17	No	3 or 5	30 min	20	70% of maximum HR	NR
Verity and Ismail [19]	59 (4)	AT: 5 CG: 5	No	3	60-90 min	16	65 to 80% of predicted HR reserve	NR

Resistance training								
Castaneda et al. [20]	66 (8)	RT: 29 CG: 31	No	3	5 exercises, 15 sets	16	60 to 80% of 1-RM	90
Church et al. [2] [b]	57 (9)	RT: 60 CG: 41	No	3	9 exercises, 21 sets	~39	Maximum weight that could be lifted 10 to 12	NR
Dunstan et al. [21]	67 (5)	RT: 16 CG: 13	Yes	3	9 exercises, 27 sets	26	75 to 85% of 1-RM (except for the first two weeks that had lighter loads)	88
Jorge et al. [6]	54 (10)	RT: 12 CG: 12	No	3	7 exercises, 4 sets, 8-12 reps	36	Maximum weight that could be lifted 8 to 12	99
Sigal et al.[16] [b]	55 (7)	RT: 49 CG: 63	No	3	7 exercises, 28 sets	26	Maximum weight that could be lifted 7 to 9 times	85
Combined training								
Balducci et al. [22]	61 (9)	CT: 51 CG: 53	No	3	60 min	52	AC: 40 to 80% of HR reserve RC: 40 to 60% of 1-RM	> 90
Balducci et al. [23]	59 (9)	CT: 288 CG: 275	Yes	2	75 min AC: RC: 4 exercises, 2-3 sets, 8-15 reps	52	Low and high-intensity groups with isocaloric sessions. AC: 55 to 70% of predicted VO_2peak RC: 60 to 80% of predicted 1-RM	80

Church et al. [2] [b]	55 (8)	CT: 62 CG: 41	No	3	AC: 106 min [c] RC: 9 exercises, 1set each	~39	AC: 64% of the VO_2peak (averaged from 9 months of study) RC: Maximum weight that could be lifted 10 to 12 times	NR
Cuff et al. [3]	63 (7)	CT: 10 (only women) CG: 9 (only women)	No	3	75 min	16	AC: 60 to 75% of HR reserve RC: loads were initially light and were progressed during the intervention	92
Dobrosielski et al. [24]	57 (6)	CT: 51 CG:63	No	3	AC: 45 min RC: 7 exercises, 2 sets, 10-15 reps	26	AC: 60 to 90% of maximum HR RC: 50% of 1-RM	92
Jorge et al. [6]	54 (10)	CT: 12 CG: 12	No	3	AC: 30 min RC: 7 exercises, 2 sets, 8-12 reps	36	Same intensity as the AT and RT programs	96
Lambers et al. [12]	56 (10)	CT: 17 CG: 11	No	3	50 min	12	AC: NR RC: 60 to 85% of 1-RM (69%, averaged from 3 months of study)	≥ 85

Loimaala et al. [25]	53 (5)	CT: 24 (only men) CG: 25 (only men)	No	4	At least 30 min of aerobic; 24 sets of resistance exercises	52	AC: 65 to 75% of VO_2peak RC: 70 to 80% of maximum voluntary contraction	NR
Sigal et al. [16] [b]	53 (7)	CT: 50 CG: 63	No	3	Both the aerobic and resistance programs	26	AC: same as aerobic training RC: same as resistance training (see above)	86
Tessier et al. [26]	69 (5)	CT: 19 CG: 20	No	3	40	16	AC: 60 to 79% of maximum HR RC: NR	> 90

Abbreviations: AT, aerobic training; RT, resistance training; CT, combined training; CG, control group; AC, aerobic component; RC, resistance component; HR, heart rate; VO_2: oxygen consumption; 1-RM, one repetition maximum; NR, not reported. [a] Exercise characteristics do not include warm up and/or cool down periods. [b] Analyses included data only from individuals who had at least 70% of adherence to the exercise programs. [c] Averaged from the actual weekly aerobic volume performed throughout the study. Age data represent weighted means and SDs between intervention and control groups.

eTable 2: Methodological quality of included studies.

	Adequate sequence generation	Allocation Concealment	Blinding of outcome	Description of losses and exclusions	Intention to treat analysis
Balducci et al. [22]	Unclear	Unclear	No	Yes	No
Balducci et al. [23]	Yes	Yes	Yes	Yes	Yes
Bjorgaas et al. [1]	Yes	Yes	No	Yes	No
Castaneda et al. [20]	Unclear	Unclear	Yes	Yes	No
Church et al. [2]	Yes	Unclear	Yes	Yes	Yes
Cuff et al.[3]	Unclear	Unclear	Unclear	Yes	No
Dobrosielski et al. [24]	Unclear	Unclear	Unclear	Yes	Unclear
Dunstan et al. [21]	Unclear	Unclear	No	Yes	No
Giannopoulou et al. [4]	Unclear	Unclear	No	Yes	No
Goldhaber-Fiebert et al. [5]	Yes	Unclear	Yes	Yes	No
Jorge et al. [6]	Unclear	Unclear	No	Yes	Yes
Kadoglou et al.[7]	Unclear	Unclear	No	Yes	No
Kadoglou et al.[8]	Unclear	Unclear	No	Yes	No
Kadoglou et al. [9]	Yes	Yes	No	Yes	No
Kadoglou et al. [10]	Yes	Unclear	No	Yes	No
Kurban et al. [11]	Unclear	Unclear	No	Yes	Yes
Lambers et al. [12]	Yes	Yes	Yes	Yes	No
Loimaala et al. [25]	Unclear	Unclear	No	Yes	No
Middlebrooke et al. [13]	Yes	Unclear	No	Yes	No
Raz et al. [14]	Unclear	Unclear	No	Yes	No
Ribeiro et al. [15]	Unclear	Unclear	No	Yes	No
Sigal et al. [16]	Yes	Yes	Yes	Yes	Yes
Sridhar et al. [17]	Unclear	Unclear	No	Yes	No
Tessier et al. [26]	Unclear	Unclear	No	Yes	No
Vancea et al. [18]	Unclear	Unclear	No	Yes	No
Verity and Ismail [19]	Unclear	Unclear	No	Yes	No

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6. CONCLUSÕES

I. O exercício estruturado, consistindo de treinamento aeróbico, resistido, ou pela combinação de ambos, por pelo menos 12 semanas, se associa com melhora do controle glicêmico de pacientes com DM2. Além disso, treinamento físico estruturado com durações superiores a 150 minutos por semana associa-se com maior magnitude de redução dos níveis de HbA1c em pacientes com DM2. Isto sugere a importância da quantidade (volume) semanal de exercício para o controle metabólico no DM2;

II. A recomendação de atividade física somente está associada com melhora do controle glicêmico no DM2 quando associada a intervenções de dieta. Ressalta-se, porém, que este resultado relaciona-se com o controle metabólico no DM2, mas não pode ser extrapolado para a prática de atividade física em outras variáveis relevantes em pacientes com DM2;

III. No treinamento aeróbico, o volume de exercício, especialmente a freqüência de sessões por semana, associa-se com as alterações nos níveis de HbA1c no DM2, indicando que o aumento no número de sessões é importante para que se alcance as metas de exercício por mais do que 150 minutos por semana;

IV. No treinamento resistido, embora a intensidade de exercício explique a heterogeneidade dos resultados entre os estudos, esta variável não se correlacionou com os efeitos deste tipo de exercício sobre a HbA1c;

V. Por fim, o volume de exercícios resistidos constituindo um programa de treinamento combinado se associa inversamente com as alterações absolutas nos de HbA1c em pacientes com DM2, indicando que este tipo de treinamento pode

promover maior controle glicêmico de acordo com a quantidade semanal de exercício resistidos.

ANEXO I

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