Masterthesis

The influence on HbA1c and weight trend of a regular sports & movement unit as part of a structured type 2 diabetes course of education

A systematic Review

submitted by

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Statutory Declaration

I declare that I have developed and written the enclosed master thesis completely by myself, and have not used sources or means without declaration in the text. Any thoughts from others or literal quotations are clearly marked. The master thesis has not been used in the same or in a similar version to achieve an academic grading and has not been published elsewhere.

Graz, am 27.03.2017 *Dr.Lejla Siljak eh*

Only with the great support and understanding of my family, friends and colleagues I was able to finish this thesis.

A special thank you goes to my daughter Amila, who has supported me throughout my whole studies, both mentally and professionally.

A special thank you also to my good friend Geraldine Niedersüß, who has helped me with her knowledge of the English language, at any time of the day.

I want to dedicate this thesis and to thank my parents Nadžija and Abdulah Jabučar, who spent their lives teaching and learning, and who have always said to me: "Study, knowledge will never let you down."

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ABBREVIATIONS

T2DM = type 2 diabetes mellitus

RCT= randomized controlled trial

PA = physical activity

MeSH =Medical Subject Heading

METS= metabolic equivalent of task

PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analysis

ADA= American Diabetes Association

For reasons of clarity, the masculine form has been used throughout this thesis, although the feminine is always also implied.

1. ABSTRACT

OBJECTIVE: The purpose of this study was to examine and systematically review the evidence of multi-component (diet and physical activity) lifestyle interventions in adults with type 2 diabetes mellitus (T2DM). It should be evaluated which effects physical activity (PA) und exercise can have on the course of T2DM, using the data available from randomised controlled trials. Healthy eating and physical activity characterise the principles of lifestyle change and associated weight loss and improved glycemic control. But ways to learn these new contents and to implement them in everyday life are not easy und have still not been found. As a part of diabetic education, a movement unit is practiced in various forms. Most interesting is the question: what remains after a completed course or medical examination and what are the benefits for the participants for the time after?

METHODS: Included and compared were randomised trials which examined the influence of different types of movement/exercise units of the important metabolic parameters and bodyweight/body composition in adults with T2DM over a length of at least 12 weeks. A comparison was made between the intervention and control group or several different intervention groups. Seven studies were included for review. Trials were identified through the Pub Med n=155, Cochrane library n=97. A search of the literature from January 2005 up to December 2016 was conducted. Eligible studies 1) recruited adults with T2DM; 2) conducted exercises (including both physical activity/aerobic and resistance training) and nutritional recommendation und or diet programs; 3) had outcomes which were reported are HbA1c and weight/BMI.

RESULTS: Of the seven studies reporting about effects of PA in T2DM, one study was a retrospective /post hoc analysis and one study was a multi-centre randomised trial (16 centres in the U.S.) There were distinct variations in the description of PA and poor reporting about nutritional intervention and results. The shortest study duration was sixteen weeks and the largest and longest follow up was interrupted after eleven years. The short-term studies of life style intervention included physical activity and diet, showing many benefits and improvements relating to glycemic control and diabetes-related coexisting illness. However, the largest long-term applications demonstrated that weight loss and fitness did not lessen the rate of cardiovascular events in overweight or obese adults with T2DM.

CONCLUSIONS: Physical activity and life style change, especially in overweight adults with T2DM, is recommended. The results of included studies validate that recommendation over a short period. The long-term data could not show improvement of the reduction of the rate of cardiovascular events in overweight adults with T2DM.

KEYWORDS: type 2 diabetes, overweight, exercise, lifestyle interventions, diet, systematic review, weight loss therapy

2. ZUSAMMENFASSUNG

ZIEL: In dieser Arbeit wurde untersucht und systematisch überprüft ob eine kombinierte (Ernährung und Bewegung) Lebensstilveränderung bei Erwachsenen mit T2DM eine Auswirkung hat. An Hand von Daten aus verfügbaren randomisierten, kontrollierten klinischen Studien, sollten die Effekte körperlicher Betätigung auf den Krankheitsverlauf evaluiert werden. Die Grundprinzipien der Änderung des Lebensstils beinhalten gesunde Ernährung und körperliche Betätigung. Jedoch wurden in Wahrheit noch keine Wege, diese neuen Inhalte zu lernen und sie im Alltag umzusetzen gefunden. Im Rahmen der in verschiedenen Formen angebotenen Diabetesschulungen wird eine Sportart als Bewegungseinheit praktiziert. Die interessanteste Frage ist was nach der Zeit der Schulung passiert und welche Vorteile für die Patienten bleiben danach.

METHODEN: Eingeschlossen und untersucht wurden randomisierte kontrollierte Studien die über den Einfluss von unterschiedlich Bewegungs-/Übungseinheiten auf wichtige metabolischen Werte wie auch auf Körpergewicht/Körperzusammensetzung bei Erwachsenen mit T2DM berichten. Es wurden eine Interventions- und Kontrollgruppe oder mehreren unterschiedlichen Interventionsgruppen in einer Dauer von mindestens zwölf Wochen verglichen. Sieben Studien wurden in den Review eingeschlossen. Die Studienidentifikation folgte durch die Datenbanken: Pub Med n=155, Cochrane library n=97. Es wurde nach Literatur aus der Zeit von Januar 2005 bis Dezember 2016 gesucht. Geeignete Studien 1) zogen Erwachsene mit T2DM heran 2) führten Bewegung- (eingeschlossen beide Arten von körperlichen Aktivitäten /aerobes Training und Krafttraining) und Ernährungsberatung und oder Diät; 3) berichteten über HbA1c und Körpergewicht/BMI Veränderungen.

ERGEBNISSE: Unter den ‚sieben in den Review eingeschlossenen Studien welche über die Effekte von körperlichen Aktivitäten bei T2DM berichtet haben, ist eine retrospektive/post hoc Studie und eine multizentrische randomisierte Studie (durchgeführt in 16 USA Zentren.) Es werden ein deutlicher Unterschied in der Beschreibung der körperlichen Aktivitäten und eine mangelhafte Beschreibung über Ernährungsinterventionen und deren Ergebnissen beobachtet. Die kürzeste Dauer war 16 Wochen und die größte und längste Studie wurde nach elf Jahren Beobachtung unterbrochen. Die kurzdauernden Lebensstilveränderungsstudien mit Steigerung der körperlichen Aktivität und Diät, zeigen viele Vorteile und Verbesserungen in Bezug auf die glykämische Kontrolle und diabetische Folgeerkrankungen. Die größte Langzeitstudie jedoch, konnte nicht beweisen dass durch Gewichtsabnahme und Verbesserung der körperlichen Fitness eine Reduktion der Häufigkeit von kardiovaskulären Ereignissen bei übergewichtigen Erwachsenen mit T2DM erreicht wird.

CONCLUSIO: Bei Erwachsenen mit T2DM insbesondere bei noch vorhandenem Übergewicht, wird körperliche Aktivität und Lebensstilveränderung empfohlen. Die Ergebnisse der angeschlossenen Studien bestätigen diese Empfehlung für die kurze Dauer. Langzeitergebnisse konnten die Reduktion der Häufigkeit von kardiovaskulären Ereignissen bei übergewichtigen Erwachsenen mit T2DM jedoch nicht bestätigen.

SCHLÜSSELWÖRTER: Typ 2 Diabetes, Bewegungseinheiten, Lifestyle Intervention, Diät, systematisches Review, Gewichtsabnahme-Therapie

3. INTRODUCTION

3.1. Rationale

3.1.1. Definition and description of diabetes mellitus

“Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels”(ADA) (1).

3.1.2. Prevalence of type 2 diabetes

The amount of people with type 2 diabetes has risen from 108 million in 1980 to 422 million in 2014.This means that the global prevalence of type 2 diabetes has risen from 4.7% in 1980 nearly doubled to 8.5% in 2014 (2). The prognosis for 2035 is ca. 600 million people with type 2 diabetes .The new “IDF Diabetes atlas” shows an estimated number of adults with diabetes worldwide and per region in 2015 and 2040 ,the prognostic increased number of persons with type 2 diabetes mellitus worldwide (3–5). (Figure 1)

There is an inverse association between socioeconomic status and the prevalence of type 2 diabetes in the middle years of life (6).

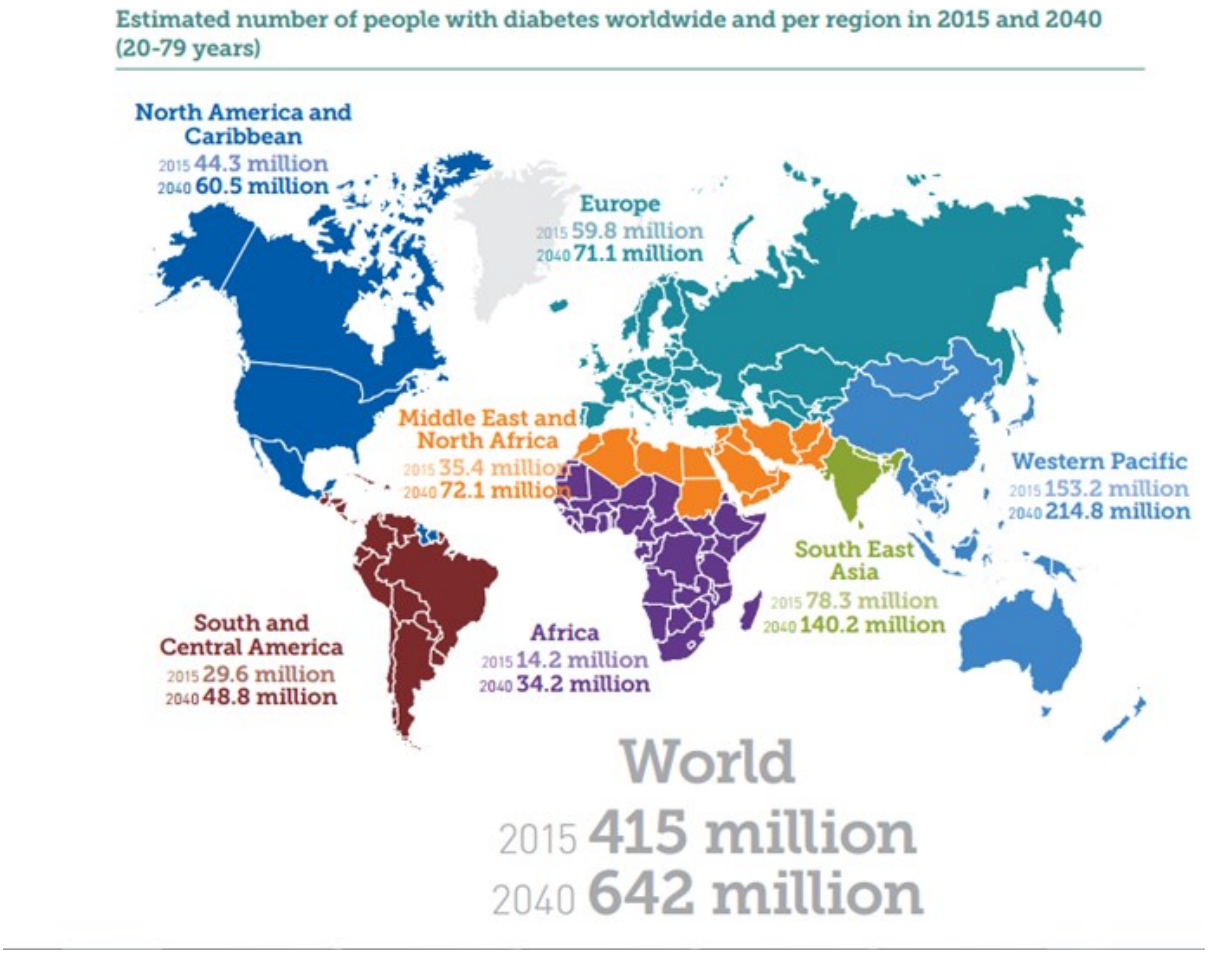

Figure 1 IDF Atlas 2015(3)

Genetic and metabolic factors have an influence on the possibility of type 2 diabetes. But the role of lifestyle, physical activity and obesity are also very important in the development of this disease. Especially obesity in particular complicates the management of type 2 diabetes by increasing insulin resistance and blood glucose levels as well as there being an increased prospect of dyslipidaemia, hypertension, cardiovascular disease and mortality (7). Since the effects of structured exercise on glycemic control have been well established, physical activity is considered a key stone in type 2 diabetes treatment. According to the recommendations of the American Diabetes Society (ADA), persons with increased diabetes risk, as well as patients with prediabetes or manifest type 2 diabetes, should be motivated to have regular moderate physical activity (30 min / day or 150 min / week (8). Type 2

diabetes is a major risk factor for cardiovascular disease (9).Exercise, as part of a healthy lifestyle, has been shown to be more effective than only pharmacological agents in progression of type 2 diabetes and developing of microvascular and macrovascular complications. Exercise and training promotion should serve as a basis in diabetes care (9). Lifestyle-based interventions with focus on nutrition recommendation, diet and physical activity remain the base of weight loss programs in general and are very important in the therapy of type 2 diabetes. The aim of this thesis is to analyse data from previous studies and to represent recent evidence on the ramification of life-style based interventions in adults with type 2 diabetes. The results of included studies validate that recommendation in short period. The long-term data could not show improvement at the reduction of the rate of cardiovascular events in overweight adults with type 2 diabetes (10).Hamman et al. based on research on adults with impaired glucose tolerance, reported that even in the absence of weight loss, physical activity alone still prevented diabetes (11)(12). Recent recommendations and guidelines include resistance training in type 2 diabetes treatment. It is based on evidence which demonstrated that there are benefits from resistance training in most metabolic parameters which are important for the development of disease and diabetes-related coexisting illness (13)(14).The second part of lifestyle intervention and a cornerstone of treatment of type 2 diabetes is dietary management. No high quality data on the adequacy of diet alone exists for treatment of type 2 diabetes mellitus (15).

In my research of relevant studies for this systematic review, I found only a small number of studies which described both exercise and diet intervention in adults with type 2 diabetes. That is not only the result of studies, but also a problem in real life.

3.2 Objective

The objective of that study was to conduct a systematic review of randomized controlled clinical trials the assessing association of structured exercise training regimens (aerobic, resistance, or both) and physical activity advice with or without

dietary intervention on change in HbA1c and bodyweight in adults with type 2 diabetes.

4. METHODS

4.1. Eligibility criteria

Included and compared were the randomised trials which examined the influence of different types of movement/exercise unit of the important metabolic parameters and bodyweight/body composition in adults with type 2 diabetes over a length of at least 12 weeks. A comparison was made between intervention and control group or several different intervention groups.

4.2. Data sources and Searches

In conformation with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (16) a search was conducted in Pub Med and Cochrane Library from January 2005 up to December 2016 and additional manual searches of bibliographies. Search results were limited to adults and studies published in English. Search filters for randomized, controlled trials (RCTs) English-language studies and free full Text were applied. The search is strategy detailed in Figure 2.

Included search words were: type 2 diabetes, exercise, nutrition. MeSH Terms were: ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields]) AND ("exercise"[MeSH Terms] OR "exercise"[All Fields]) AND ("nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields]) AND ("2005/01/01"[PDAT] : "2016/12/31"[PDAT]) AND Randomized Controlled Trial[ptyp]

4.3. Study Selection

Following the search, duplicates were removed and screened titles and abstracts for relevant articles based on eligibility criteria. Studies were included if they: (i) were conducted on adults with clinically diagnosed type 2 diabetes mellitus; (ii) reported on intervention outcomes from randomised trial; (iii) included well-documented aerobic, fitness or progressive resistance training exercise with or without nutritional intervention;(iv) had comparison groups which could be control/usual care or other intervention groups. Studies were excluded if: (i) intervention duration was short<12weeks; (ii) they did not report about face to face support, only self-management or online support was reported; (iii) they reported about only theory-based intervention; (iv) they primarily compared different dietary composition; (v) they did not report about HbA1c and weight change outcomes; (vi) they included only one gender group; (vii) they were not available in full text. All randomised controlled trials compare any type of well-documented aerobic, fitness or progressive resistance training exercise in people with type 2 diabetes mellitus. The study participants are adults with type 2 diabetes and are able to take a part in moderate physical activities.

4.4. Data collection process

Characteristic and results the studies were extracted by one Author (L.S.), from each study and a list of data extraction topics for the studies included in this systematic review was developed. These items were: author's name, year of publication, country, study design, journal name, participants, intervention groups, intervention length, follow up, description of intervention, description of dietary intervention, description of statistical analyse, outcome measures, results of diabetes markers and weight and retention. Table 2 (Characteristic of Included Studies) and Table 3. (Results of Included Studies).

4.5. Data items

Variables for which data were sought were based on PICO questions (17) and included:

Participants	Adult with type 2 diabetes mellitus and overweight
Intervention	Lifestyle intervention with diabetes education and exercise with professional staff and with or without nutritional component.
Comparison	Control group with another movement program or without program
Outcome	Control of important laboratory and anthropometric parameter, prognostic value for cardiovascular risk

4.6. Risk of bias in individual studies

The methodological quality of the admitted studies was evaluated with an established quality score (0–10). The CONSORT statement for randomized controlled trials was used as a tool for adjustment (18). One point was awarded for each present item and each item scored as 'absent' or 'unclear or inadequately described' were awarded with zero points. Each study was assigned a risk of bias category based on the following thresholds for quality scores: high risk (0–3), moderate risk (4–7) and low risk (8-10). The methodological quality items included: (1) power calculation was reported ; (2) randomization adequately characterised and carried out; (3) Inclusion of a control group; (4) Baseline results reported separately for each group; (5) did the study analyses account for potential differences at baseline? (6) assessor blinding; (7) intention-to-treat analysis;(8) Dropout ≤20% for ≤6 months intervention and ≤30% for >6 months follow-up accounted for in analyses; (9); the study report summary results for each group;(10) Summary results presented with effect sizes and precision estimates.(Table 1)

Risk of bias across studies

The 10-item risk of bias analysis conclusion for seven admitted studies are displayed in Table 1. Five trials (10,19–22) were assessed as having low risk of bias; two trials (23,24) were assessed as having moderate risk of bias . Five studies had reported about Power calculation and were adequately powered (10,19–22). Randomization was acceptably described and carried out in five studies (10,19–21,23). All trials have a control group from randomised participants and the baseline results was reported separately for each group and all studies analysed account for potential differences at baseline. Two studies describe blinded assessor (19,23), and five studies did not report about. Four trials used an intention to treat analysis (10,19–21) and four trials had drop out ≤20% for ≤6months intervention and ≤30% for >6months follow-up (10,21,24). Only one trial did not have summary results for each group (19). Summary results were presented with precision estimates and/or effect sizes in four trials (19–22).

5. RESULTS

5.1. Selection and Description of Included Studies

The search identified 911 records on Pub Med, 97 at Cochrane library and three studies were found from the reference lists of the manuscripts retrieved. After a selection of control randomised trials and duplicates 224 records were screened. From these 166 records were excluded based on title/abstract and free full text eligibility leaving 37 full-text articles for review. (Figure 2). Thirty full-text articles were excluded for the following reasons: only weight loss or diet or exercise intervention was described (n=6), participants were included who did not have type 2 diabetes, they were studies on risk- or prevention (obesity, prediabetes, risk or prevention (n=9), only dietary intervention was dealt with (n=1), special marker in fat tissue or maker of inflammation were primary outcome points (n=3), no results were described (n=4), HbA1c and weight was not observed (n=1), specific group was observed (only women) (n=2), no free text (n=3), special inclusion criteria

(comorbidity hypertension) (n=1), short observation period or low number of participants(n=2). This left seven studies based on nine publications for review(19–25). One trial was associated with several publications, with different reports about baseline characteristic, primary outcome or follow up. Detailed design, sample and intervention characteristics of included studies are shown in Table 2.and 3.

The duration of intervention ranges from 16 weeks to 4 years. Follow ups were reported in four studies between 12 months and 11.5 years (10,19,21,22).The seven studies included between 58 and 5145 participants. The majority of the participants were previously inactive adults with type 2 diabetes. When combined, 5980 individuals (2318 male; 3306 female; 356 not reported) participated in the trials. The reported mean (range) participant age was 60.7 (55.5-75) years (10,19,23,24).Three studies did not report about gender proportion, an absolute mean range proportion of female participants is not available (20–22). Only one trial included parallel adults with type 2 diabetes and overweight adults without diabetes. The results from either group were indeed incorporated in report (23). The description of dietary methods is available in 5 trials (10,19–22).One study combined progressive resistance training and a high protein diet (20) and the other studies included dietary guidance. Nearly all (6/7) studies delivered their interventions via group or individual or combined group/individual face- to-face sessions. Only one study was a post hoc analyse from a self-managed physical activity program. Five studies compared lifestyle intervention with an intervention comparison group (10,19–21,23).One study made a comparison between one non activity group (control group) and six groups with different exercise intensity levels (22). One study observed one training group under supervision and one control group that followed a concise education program, but were given no coaching (24). Power- or resistance training was included in three studies (19,20,23), one study compared brisk walking and resistance training (21). All studies reported on HbA1c and weight trend or BMI as a primary outcome (10,19–22,24). The results for diabetes marker and weight was reported in all studies (10,19–24). Only one study described the consequences of better body fitness on social and medical costs (22). All studies described the drop out on average of between 15 and 98 percent (10,19–24).

5.2. PRISMA 2009 Flow Diagram

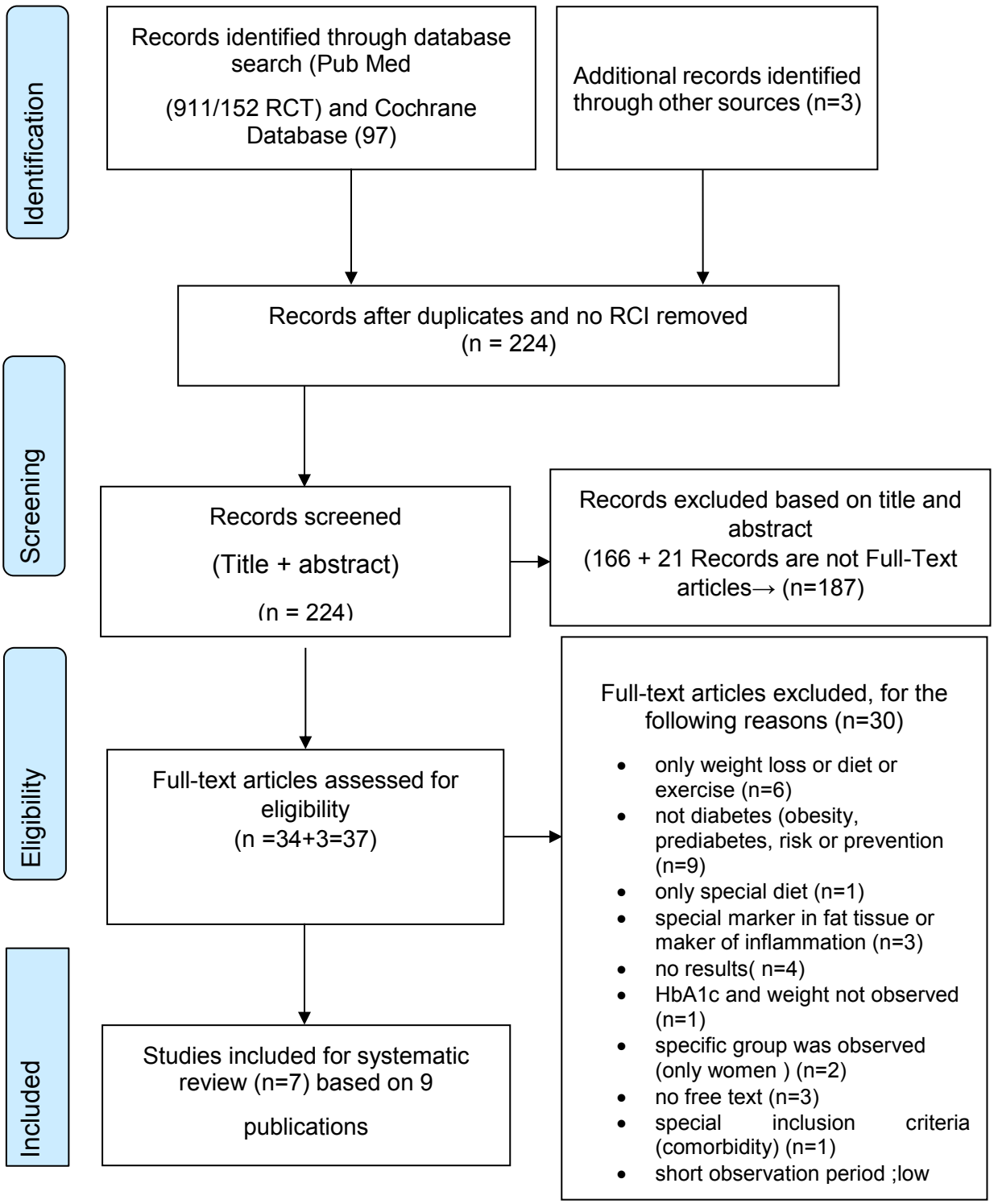

Figure 2 "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow of study selection" (16)

Muscle-cell metabolism is very important in type 2 diabetes. Figure 3 shows "mechanisms of exercise-stimulated glucose uptake in skeletal muscle" (26).

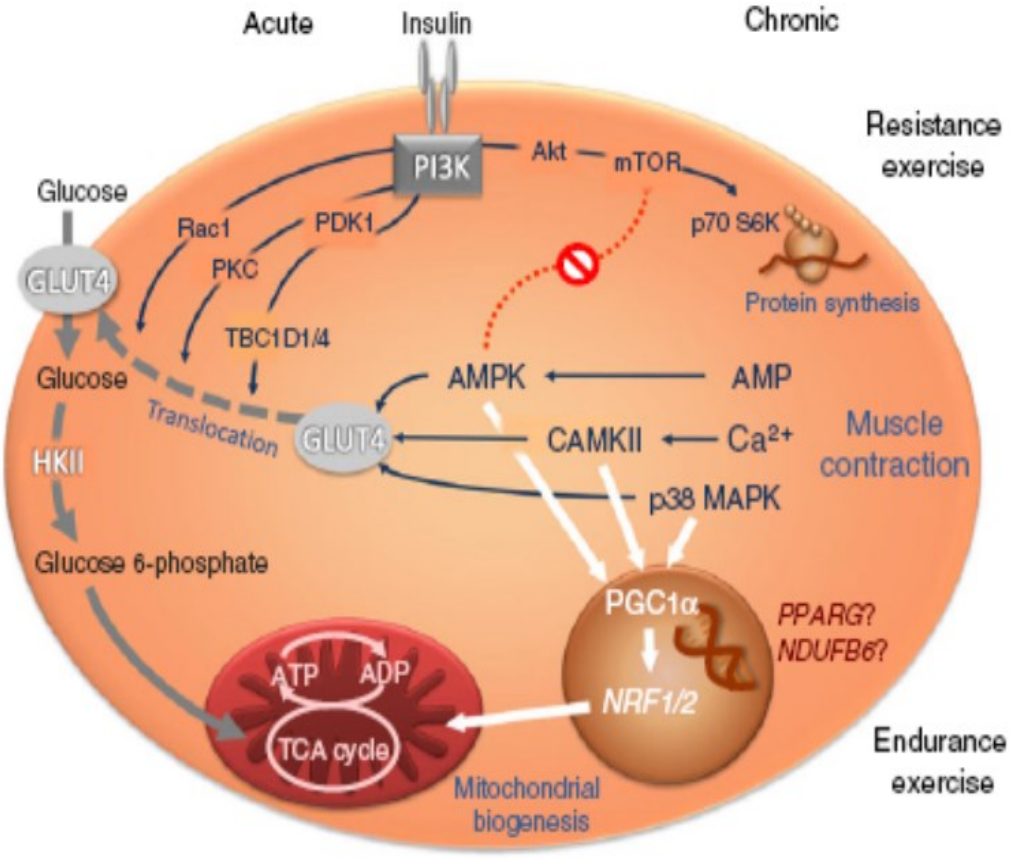

Figure 3 Glucose and exercise (26)

Several metabolic processes happen in the skeletal muscle upon acute or chronic type of muscular contraction. Muscle cell and cell organelle like the mitochondria, and the endoplasmic reticulum are involved in the metabolism circle. It depends on the type of exercise (acute, chronic, resistance or endurance exercise) which enzyme will be activated. Acute endurance exercise activates protein kinase. Glucose transporter 4 is translocated and insulin-independent glucose transport facilitates.

"Post-exercise effects involve activation of peroxisome-proliferator activated receptor-γ coactivator 1α (PGC1α), which by stimulating expression of nuclear respiratory factors (NRF1, NRF2) will increase ATP synthesis and, later,

mitochondrial biogenesis. In addition, exercising improves insulin-dependent glucose transport and phosphorylation by hexokinase II (HKII), which includes more distal components of insulin signalling such as phosphoinositide-dependent kinase 1 (PDK1), TBC1 domain family, members 1 and 4 (TBC1D1/4), Rac1 and protein kinase C (PKC) isoforms. The effects of training on mitochondrial function and glucose metabolism may be modulated by variants intense such as PPARG or NDUFB6. While the cellular mechanisms of acute resistance-type exercise are less clear, chronic resistance training activates the mammalian target of rapamycin (m TOR)/serine kinase 6 (S6K) pathway, ultimately leading to protein synthesis and increased muscle mass. TCA, tricarboxylic acid" (26).

5.3. Study characteristics

5.3.1. "Graded Resistance Exercise and Type 2 Diabetes in older adults (The GREAT2DO study): methods and baseline cohort characteristics of a randomized controlled trial (GREAT2DO Study) " Simpson et al. 2015 (19)

Qualification criteria for this study included community-dwelling participants, male and female, previously diagnosed with type 2 diabetes and the metabolic parameters which describe the current definition of metabolic syndrome according to the International Diabetes Federation. 103 participants (48.5 % women, 71.6 ± 5.6 years) were involved in the study. The type 2 diabetes was diagnosed for 8 ± 6 years and participants had a body mass index of 31.6 ± 4.0 kg/m². Fasting glucose and insulin were 7.3 ± 2.4 mmol/L and 10.6 ± 6.3 mU/L, HbA1c was 54 ± 12 mmol/mol. (12±3.2%).Participants were treated with diet only, oral medication, insulin or combination of those at the start of the study (19).

The essential hypothesis affirmed that power training will be associated with sustained improvement in insulin sensitivity and HbA1c.The results were compared between the group with power training and the sham exercise control group at a half year and one year follow-up. Secondary effects were all important characteristics of metabolic syndrome. Body composition, measures of energy expenditure, muscle morphology and metabolism, genetic and epigenetic markers connected to metabolic/cardiovascular health and exercise adaptation, adipokines, and fat

oxidation, neuropsychological function, cardiovascular health status, quality of life, dietary intake and habitual physical and sedentary activity levels were measured. Participants were randomised in two groups: a) participants under full supervision and power training intervention n=49 and b) sham exercise control group n=54. Intervention group participants had the whole body machine-based power training three times per week. The control group practiced the same volume of non-progressive, low-intensity training in the same facility, three times per week. The group was coached by the same trainers, and had three sets of eight repetitions on the same machines but no loading beyond the weight. The assessment was conducted at a baseline of six months and followed one year. Follow up was six years, and the participants were advised to exercise at a moderate-high intensity. All assessors were blinded and the outcome measures were administered at baseline, six month and one year. Nutritional habits were noted with a food frequency questionnaire over the past four months. The statistical methods are described in detail. Follow up is six years, 35 (34%) participants completed it, remaining six participants scheduled for the final assessment (19).

The conclusion at the primary outcome showed mean change at HbA1c from -13.1 mmol/mol (-3.3 %). Mean change of insulin resistance measured with HOMA 2IR (72 hours and 96 hours post exercise) was -0.6. Glycemic control can be improved with power training and that maybe the attainable adjunctive therapy for the growing epidemic of T2D in older adults (19). Authors claim that no study investigating high intensity training has yet been published. “The GREAT2DO will provide the first evidence of the safety and efficacy of resistance training in older adults with type 2 diabetes”(19).

5.3.2. “Adoption and maintenance of gym-based strength training in the community setting In adults with excess weight or type 2 diabetes: a randomized controlled trial”

Megan Teychenne et al.2015 (23)

This study can be described as a behaviourally focused, community-based, enhanced strength training program intervention. Being overweight is recognised as

a major risk factor for acquiring type 2 diabetes (23,27). Due to initial recruitment complications, the target group was expanded to also fit in those who were classified as being overweight (BMI >25) and not currently performing strength training (ST). Male and female participants aged 40–75 years old (n = 318), who had type 2 diabetes (>3-months) (n = 117) and participants with BMI >25 (n = 201) and not currently performing strength training were recruited. 131 woman and 187 men, aged 40–75 years were included in the study. The participants were randomised in two group: EST –enhanced strength training program (n=156) and SST -standard strength training program (n=162). There were 49 (31%) participants with diagnosed type 2 diabetes in the standard strength training group and 68 (42%) in the enhanced strength training group. The weight of participants in the standard strength group was (kg) 93.4 ± 17.3 and in the enhanced strength training group 93.1 ± 19.5, standard strength training group BMI (kg/m2) was 33.2 ± 5.4 and at the enhanced strength training group 33.7 ± 6.7. The HbA1c (%) of the standard strength training group was 6.0 ± 0.7 and of the enhanced training group 6.3 ± 1.0. Twenty one participants of the standard training group (14 %) and 43 (27 %) participants of the enhanced strength training group were treated with oral hypoglycaemic medication. Insulin therapy was used by two participants of the standard strength training group (1 %) and two participants (1 %) of the enhanced training group. Seven participants (5 %) of the standard strength training group and four participants (3%) of the enhanced strength training group were treated with a combination of both. Applicants in the standard strength training intervention group (n = 156) followed a commencing eight-week program, based on the *Lift for Life*® program (23,28).

“Adoption and maintenance were defined as undertaking ≥ three weekly gym-based exercise sessions during the first half year respectively and were assessed using a modified version of the CHAMPS (Community Healthy Activity Models Program for Seniors) instrument”(23,29).Outcome variables were : HbA1c (%),weight (kg), BMI (kg/m²),upper body strength (kg), lower body strength (kg), leisure-time physical activity (%)(23). Dietary intervention was not describe.

“Relative to the SST group, the adjusted odds ratio (OR) of adopting ST for all participants in the EST group was 3.3 (95 % CI 1.2 to 9.4). In stratified analyses

including only those with T2DM, relative to the SST group, the adjusted OR of adopting ST in the EST group was 8.2 (95 % CI 1.5–45.5). No significant differences between the groups were observed for the maintenance of ST in either pooled or stratified analyses. In those with T2DM, there was a significant reduction in HbA1c in the EST compared to SST group during the adoption phase (net difference, -0.13 % [-0.26 to -0.01]), which persisted after 12-months (-0.17 % [-0.3 to -0.05])"(23). That shows a more efficient effect of the enhanced strength training program on the adoption of strength training in comparison to a standard strength training program in a community-based health and fitness facility, in overweight adults and those with diabetes"(23).

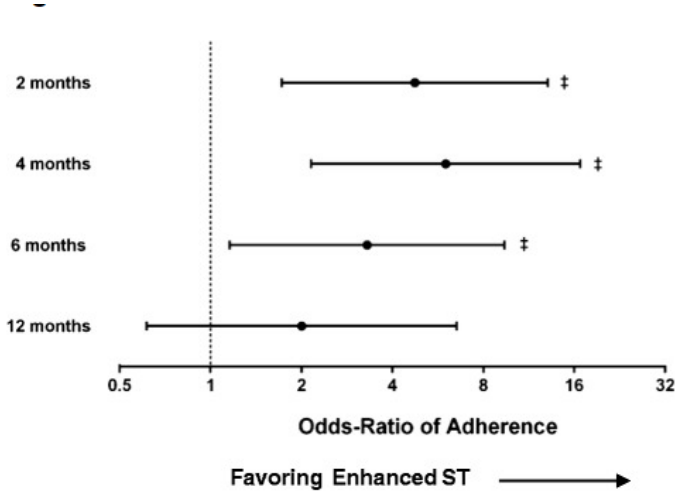

Figure 4 "Forrest plot showing odds ratio of adherence to strength training at 2-, 4-, 6- and 12- months*. * based on the mixed model with random effects; Adherence = ≥3 sessions per week. ‡ $p < 0.05$ difference between the Enhanced and Standard ST group" (23)

5.3.3. “The Look AHEAD Study”

The Look Ahead Research Group 2006-2013 (10,25,30) included three papers:

- “Baseline characteristics of the randomized cohort from the Look AHEAD (Action for Health in Diabetes) Research Study ; The Look AHEAD research group” (10)
- “Long Term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes: Four Year Results of the Look AHEAD Trial” (30)
- “The development and description of the Comparison group in the Look AHEAD trial :The Look HEAD research group” (25)

The Look Ahead (Action for Health in Diabetes) Study was a multicentre (16 centre) randomised clinical trial. The study included overweight and obese adults with type 2 diabetes and was designed to appraise the long term effects (up to 11.5 years) of a concentrates weight loss intervention on the time to incidence for major cardiovascular events (10). Eligibility criteria for this study included diagnosis of type 2 diabetes (determined by self-report and verification), adults of age 45–74 years, BMI >25 kg/m2 (>27 kg/m2 if currently taking insulin). The 5145 participants with an average age at entry of 59 ± 6.8 years (mean ± SD), and 60% women were included. There were 14.6% of participants who were taking insulin at the time of randomization. The participants were 63.3 %white, 15.6% African-American, 13.2% Hispanic, 5.1% American Indian, and 1.0% Asian-American. Overall, BMI averaged 36 ± 5.9 kg/m² at baseline. About one quarter of men and women (20.2 to 27.6%) had an HbA1c < 6.5%.14.1 % participants had a history of cardiovascular disease. Only a small number (8% overall) had HbA1c values that were > 9%.(10) “Participants were randomised in two groups: a) Diabetes Support and Education (DSE) and b) Intensive Lifestyle Intervention (ILI). All study participants were required to complete a two-week run-in period prior to randomization which required successful self-monitoring of diet and physical activity. The intensive lifestyle intervention

includes moderate-intensity physical activity to achieve and sustain at least 200 min per week of exercise together with a healthy diet that includes portion-controlled foods" (31). Participants were advised to engage in brisk walking or similar aerobic activity. The lifestyle intervention had three phases:

- phase I months: 1-6 with weekly on-site visits; three group and one individual session; exercise ≥175 min/week by month six;
- months 7-12 : three on-site visits per month; two group and one individual session ; increase minute per week of activity; 10000 steps/day goal
- phase II years 2-4 :minimum of one on-site visit per month; one individual session with minimum of one additional contact by phone, mail or
- e-mail; maintain high level of physical activity
- phase III year 5+ : on-site visits monthly recommended; individual treatment sessions; prevention of inactivity (31)

The Look AHEAD Study described short- and long-term result of lifestyle modification. The trial was interrupted when the median follow-up was 9.6 year. The intensive lifestyle intervention produced greater weight loss and greater reductions in HbA1c. Just the low-density-lipoprotein cholesterol level did not decrease. Figure 5 shows changes in weight, physical fitness, waist circumference and HbA1c in a ten years follow-up. It seems that the changes in weight, waist circumference, physical fitness and glycemic control had a maximal change in the first year of intervention, followed by gradual regain. Several studies of multicomponent lifestyle interventions confirmed the same results (32,33). The initial improvements in fitness and cardiovascular risk factors in the intervention group is also greater. "The Look AHEAD study reported that participants in the intervention group had a partial remission of diabetes during the first 4 years" (34) as well as other benefits like reduction of urinary incontinence (35), sleep apnoea (36), and depression (37). The mobility, physical activity and the quality of life were improved.

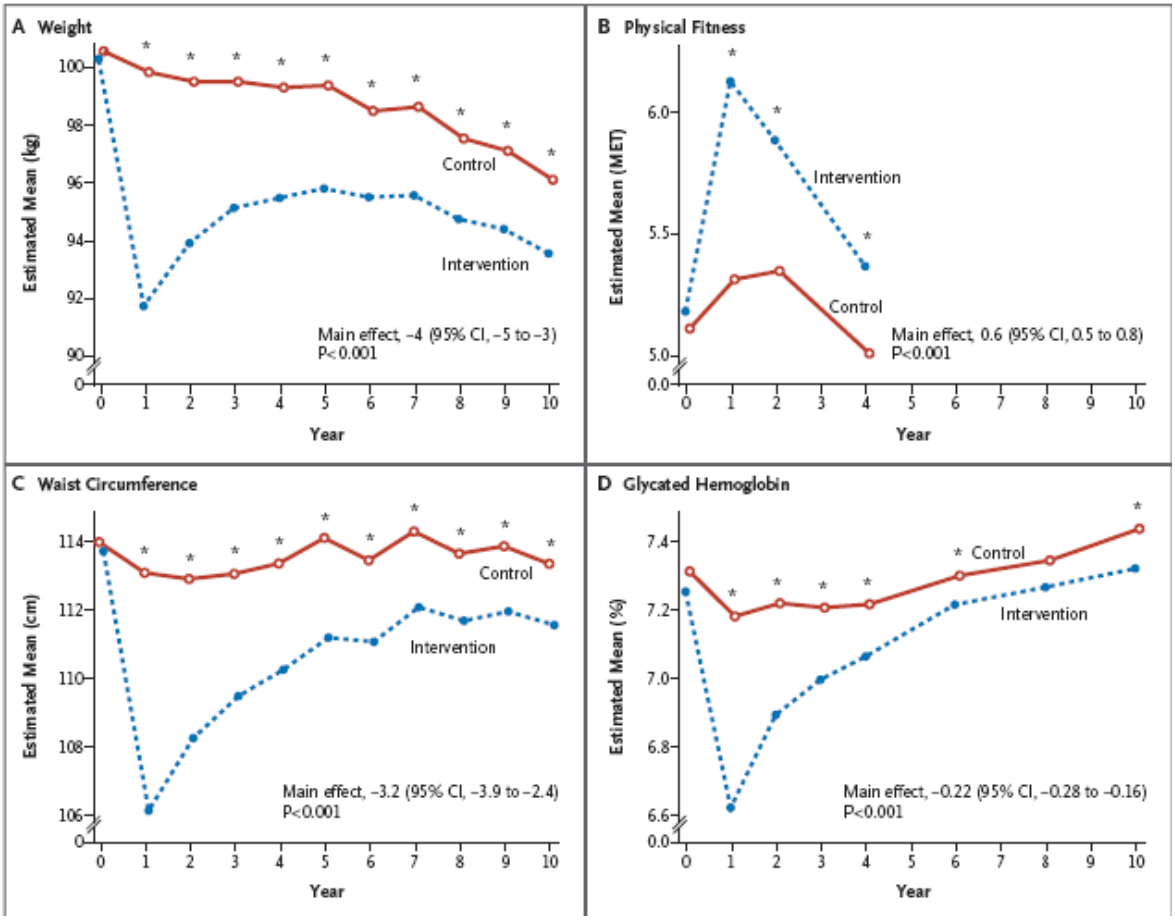

Figure 5 "Changes in Weight, Physical Fitness, Waist Circumference, and HbA1c Level during 10 Years of Follow-up in Look AHEAD Study" (33)

5.3.4. "A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes"
Wycherly T.P. et al. (20)

The participants of the study were 83 men and women with type 2 diabetes. The main age was 56.1 ± 7.5 years, BMI 35.4 ± 4.6 kg/m^2.One group got an isocaloric, energy-restricted diet (female subjects 6 MJ/day, male subjects 7 MJ/day) of either standard carbohydrate (CON; carbohydrate: protein: fat 53:19:26).The second group got high protein diet (HP; 43:33:22) with or without supervised resistance exercise training (3 days/week). Body markers like weight and body composition, waist circumference, and cardio metabolic risk markers were assessed. The study went on for 16 weeks. The primary objective of the study was to evaluate difference between two low-fat hypocaloric diets differing in the carbohydrate-to-protein ratio,

on cardiovascular disease risk outcomes in overweight and obese patients with type 2 diabetes. Weight loss and body composition were also observed. The participants were matched for age, sex and weight, then randomised to one of four lifestyle interventions:

- 1.CON energy restricted standard carbohydrate low-protein, low-fat diet alone
- 2.CON +RT(resistance training)
- 3. HP (high protein) isocaloric higher-protein, moderate –carbohydrate, low-fat alone
- 4. HP+ RT:

“RT=progressive resistance training with eight separate exercises (leg press, knee extension, chest press, shoulder press, latissimus pull down, seated row, triceps press, and sit-ups)” (20).

Outcomes in body weight, body composition, muscle strength, serum lipids and insulin, plasma glucose, C-reactive protein, creatinine and HbA1C, blood pressure were measured. It was no significant effect of age or sex for any of the outcomes observed. Statistical analyses were performed using SPSS for Windows. A total of twenty four out of 83 randomized participants did not finish the study (18 withdrew and six participants were excluded for dietary noncompliance). The study was completed with fifty-nine participants. Through this study it was possible to show that a structured, energy-restricted diet as a part of lifestyle intervention can make improvements in glycemic control cardiovascular risk factors in a resistance training program in obese participants with type 2 diabetes and sedentary lifestyle. “The addition of RT increased weight and fat mass loss, which was further magnified by replacing some dietary carbohydrate with protein” (20).

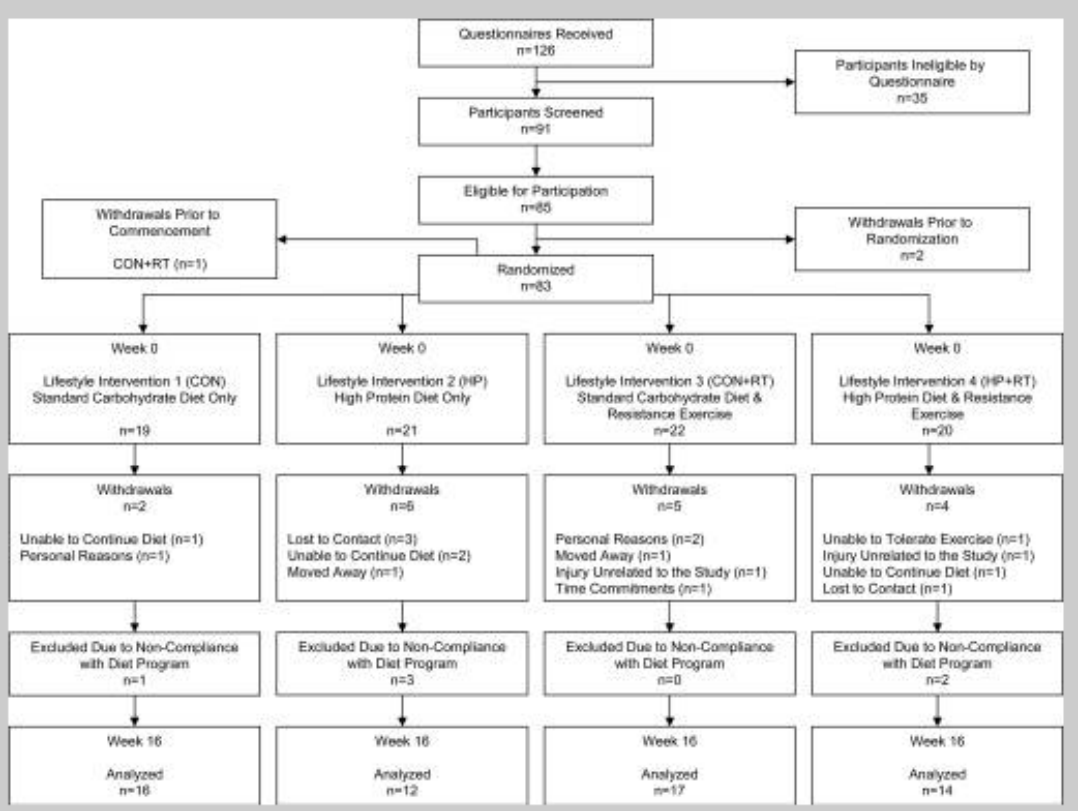

Figure 6. Participant flow in the study (20)

5.3.5. “Brisk walking compared with an individualised medical fitness programme for patients with type 2 diabetes: a randomised controlled trial”

Praet S.F.E et al. 2008 (21)

This study randomised 92 type 2 diabetes patients (60 ± 9 years old) in two groups. One of them performed 60 minute brisk walking, three times a week ($n = 49$).The second group performed 60minutes of a medical fitness program ($n = 43$). “Primary outcome was the difference in changes in HbA1c values at 12 months. Secondary outcomes were differences in changes in blood pressure, plasma lipid concentrations, insulin sensitivity, body composition, physical fitness, program adherence rate and health-related quality of life” (21). Dietary intervention was not described. The brisk walking group and the medical fitness group had a concisely explained schedule and were supervised three times a week by certified trainers

and a physiotherapist during the first three months. After three months the physiotherapist visited the group on a consultation basis. Group sizes varied between fifteen and twenty-five participants. It was a dropout of fifty and twenty-five percent in both groups. The main reason for the dropouts were overuse injuries and lack of motivation. The participants had to absolve three, sixteen minute sessions, of brisk walking weekly. The resistance type exercise training was gradually increased consisting of floor exercises and resistance using individual body weight and elastic bands. There were three exercise sessions of the medical fitness program per week. Endurance type exercise consisted of, a home trainer exercise and resistance type exercise with a selection of eight different exercises for upper and lower body muscle groups. The medical fitness program was progressively increased from three times of half an hour per week (90 min/week) towards a total of 180 to 225 min per week. Twenty-seven of ninety-two participants (29%) completed a twelve months follow-up. The results showed that changes in HbA1c values following the prescription of brisk walking or medical fitness intervention were identical (95% CI −0.42, 0.43; p=0.99)**.** Those participants who had to be prescribed higher doses of blood glucose-lowering medication through the follow-up period from ITT analysis, were excluded. BMI did not change. "This means that the modulation of glycaemic control and cardiovascular risk in type 2 diabetes through the prescription of group-based brisk walking represents an equally effective intervention when compared with more individualised medical fitness programs"(21). Overuse injuries and motivation problems should be reduced in the future exercise intervention programs.

5.3.6. "Make Your Diabetic Patients Walk"

Di Loreto C.et al. 2004 (22)

Eligibility criteria for this study contained the diagnosis of type 2 diabetes of at least two years and age >40 years before recruitment. The excluding criteria were: illnesses that could seriously reduce life expectancy or cause cardiac-, liver-, or renal failure. 182 Participants (age 62 ± 0.7 years, 88 men and women, diabetes

duration 7.6 ± 0.3 years) were including to the study, which finished in December 2002. Only three attendants did not complete the study. The study is a post hoc analysis. It was observed which long-term effects of increased energy expenditure through aerobic physical activity exist. There were six groups of participants based on their increments in METs per hour per week and they were followed for two years. The groups were divided in the following way: “group 0 (no activity, n =28), group 1–10 (6.8 ±0.3 METs /h/week, n = 27), group 11–20 (17.1±0.4, n=31), group 21–30 (27.0 ±0.5, n =27), group 31– 40 (37.5 ± 0.5, n = 32), and group >40 (58.3 ±1.8, n= 34), including all the subjects who achieved change in energy expenditure >40 METs/ h/ week” (22).

Follow up was 2 years. “The diet suggested that all patients contained 55% of calories from complex carbohydrates, 30% from fat, and 15% from protein. Overweight and obese patients were given a diet with a negative balance of ∼300 kcal/day, including in the calculation the energy expenditure due to voluntary physical activity. Table 3 shows the results of change for diabetes marker, blood pressure, cholesterol and triglycerides-level of each group” (22). There were no significant changes in any of the health parameters examined in groups 0 and 1-10 and significant reductions in higher groups. The study also shows consequences in medical or indirect costs after two years.

Walking, h/week	0	1,5	4	5,5	7,5	12
Bodyweight, kg	+0.8	+0.6	+0.1	-2.2	-3.0	-3.2
Waist circumference cm	+1.0	+1.0	-0.9	-3.8	-5.5	-7.1
HbA1c %	+0.03	-0.06	-0.44	-0.88	-1.11	-1.19
Blood pressure sys mmHg	-1.8	-1.5	-6.4	-5.5	-6.6	-9.2
Blood pressure dia.mm Hg	-4.6	-2.4	-2.9	-4.8	-5.3	-7.1
Cholesterol , mg/dl	-3.8	-5.6	-10.2	-10.7	-7.4	-10.9
LDL chol., mg/dl	-4.5	-7.1	-3.4	-5.3	-6.3	-7.7
HDL chol.,mg/dl	+0.1	+1.1	+2.9	+5.6	+10.4	+6.3
Triglycerides mg/dl	+3.4	+2.1	-48.2	-55.2	-57.4	-68.4
CVD Risk %	+0.1	-0.3	-2.6	-3.7	-4.8	-4.3

Figure 7. Effects of physical activity on cardio metabolic parameters (22)

5.3.7. "Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients"

Ligtenberg P.C., Hoekstra J.B.L., Bol L E., Zonderland M.L.,Erkelen D.W.1997 (24)

A total of 58 participants, 38 woman and 20 man, (mean age: 62±5years; range: 55-75years) with type 2 diabetes were randomized to a physical training or a control program. The training program was held three times a week. The intensity of work was set at 60-80% of Vo2max, monitored on the basis of the heart rate, and was based on the recommendations of the ADA. It consisted of exercising major muscle groups. Three phases of program were described: phase 1) six week group training

under direct supervision, phase 2) six week training at home individually (contact once over two weeks), phase 3) training at home without being contacted by the investigator. The control group followed one educational program. There was no follow up. Dietary intervention was not described. All participants were briefed to keep their usual physical activity and diet. It was a questionnaire of habitual physical activity, and diet recording by a 3-day record method (24). Fifty-one of fifty-eight participants (88%) completed a 26 weeks study. Outcome measures were: HbA1c, fasting C-peptide, cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoprotein A+B and body weight. Detailed results are shown the Table 3. “Physical training in obese type 2 diabetic patients over 55years of age does not change glycaemic control or insulin sensitivity in the short term” (24).

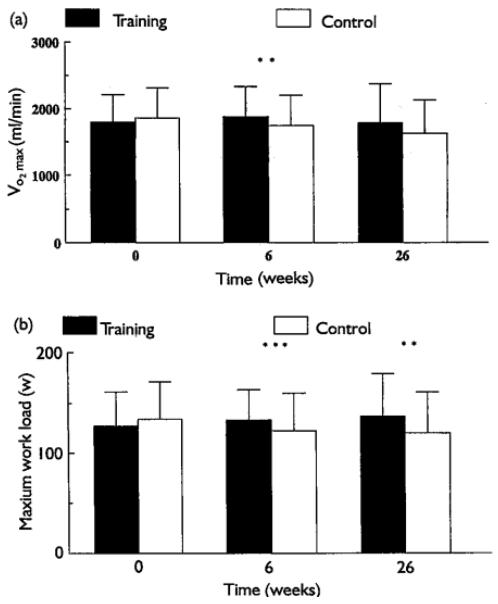

Figure 8. “Maximal oxygen uptake (Vo2max) reached in ml/min (a) and maximum work load reached in watts (b) during cyclometer exercise testing in training and control group. For (a) **P≤O.OI between groups (MANOVA), means±SD are given. For (b) **P≤O.O1 between groups(MANOVA); ***P≤O.OOI between groups (MANOVA); rneans ±SD are given” (24)

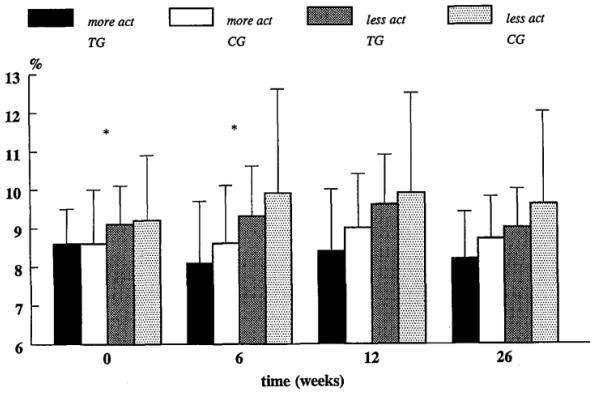

Figure 9. “HbA1c levels subdivided into four groups [previous more active in training group (TG), previous more active in control group (CG), previous less active in training group, previous less active in control group]. *P<0.05 between groups with previous more and less activity (MANOVA); means± SD are given” (24)

Table 1.”Methodological quality score and risk of bias assessment in lifestyle-based intervention trials in adults with type 2 diabetes”(18)

Author	year	Study Name (SN)	Power calculation reported	Randomization adequately described	Inclusion of a control group	Baseline results reported separately for each group	Potential differences at baseline were accounted?	Assessor blinding	Intention to treat analysis was used in the study?	Dropout ≤20% for ≤6m intervention and ≤30% for >6m follow-up	the study report summary results for each group	Summary results presented with effect size and precision of the estimates	Total Score (/10) (risk of bias)
Kylie A,Simpson etal.(19)	2015	The GREAT2DO Study	1	1	1	1	1	1	1	0	0	1	8/10(low)
Teychenne M. et al.(23)	2015	STRONG Study					0					1	1
The Look AHEAD Research Group(10,31,33)	2012	Look Ahead Study					1					1	1
Wycherley T.P. at al.(20)	2010						1					1	1
PraetS.F.E et al.(21)	2008						1					1	1
Di Loreto C. et al. (22)	2004						1					0	1

(continued at the next page)

Table 1.”Methodological quality score and risk of bias assessment in

	year	Study Name (SN)	Power calculation reported	Randomization adequately described	Inclusion of a control group	Base res repo sepa for e gro
Ligtenberg P.C.Hoekstra J.B.L. Bol L E. **Zonderland M.L. Erkelen D.W.** (24)	1997		0	0	1	1

high risk (0–3), moderate risk (4–7) and low risk (8-10) based on CONSORT statement.

1 One point awarded for item scored as “present”
0 Zero points awarded for item scored as “absent”,
? Zero points awarded for item scored as “unclear or inadequately described”

Table 2. Characteristic of Included Studies (continued at the next pages)

Author, year and study name Country	Design journal name	Participants	Intervention groups (n) Intervention length Follow up	Description of dietary intervention	Description of physical activity intervention
Simpson et al. 2015 SN: GREAT2DO Australia (19)	RCT Bio Med Central TRIALS	T2DM n*=103 M: n=53 F: n=50 n~ = 86 Age (mean ± SD) =71.6 ± 5.6	Groups Power training INT n=49 and Sham exercise CG n=54 Intervention length 1 yr. Mode Group face to face Follow up 5 yr.	"Food frequency questionnaire over past 4 months"(19)	Power training group: 3 days per week , (3 sets of 8 repetitions) Sham exercise group: Same facility, 3 days per week, same trainers, 3 sets of 8 repetitions on the same machines no loading beyond the weight
Teychenne M.et al. 2015 **(SN) :STRONG Australia** (23)	RCT The International Journal Of Behavioural Nutrition And Physical Activity	T2DM Overweight n* = 318 M=187 F: 131 n~= 47 Age 55.5 ± 8.6	Groups with T2DM and without T2DM EST n=162 SST Group n= 156 Intervention length 1 yr. Mode group face to face Follow up nil	not reported	SST intervention group: eight-week Lift for Life program®. Two time a week (45–60 mins) group exercise sessions with supervision EST: Standard Lift for Life® program and motivationally tailored behavioural counselling and print information.
"The Look AHEAD Research Group"(10,25,30) **2012 (SN): Look AHEAD Study** (10,31,33)	RCT Diabetes & vascular disease research (2006) The new England journal of medicine(2013) Clinical Trials (2011)	T2DM n= 5145 F: 60 % Age: 59 ± 6.8 years (mean ± SD), BMI averaged 36 ± 5.9 kg/m2	Groups ILI (intensive lifestyle intervention) n= 2570 DSE (diabetes support and education) n=2575 Intervention length 4 yr. Mode Group and individual face to face Follow up 11,5 yr.	**first week** self-selected diet of conventional foods **second week** similar diet but restrict intake persons < 114 kg (250 lb) 1200−1500 kcal/d individuals ≥ 114 kg 1500−1800 kcal/d < 30% of calories from fat, with < 10% from saturated fat.	lifestyle intervention versus enhanced usual care First half of the year: one individual session and three group sessions per month and nutritional support. Second half of the year: one individual and two group meetings per month Year2-4:individual basis treatment , one on-site visit per month and a second contact by telephone, mail, or e-mail. After year 4: monthly individual visits, one refresher group and one campaign a year

Table 2. Characteristic of Included Studies (continued)

Author, year and study name Country	Design journal name	Participants	Intervention groups (n) Intervention length Follow up	Description of dietary intervention	Description of physical activity intervention
Wycherley T.P. at al. 2010 Australia (20)	RCT Diabetes Care (2010)	T2DM Overweigh sedentary n* = 82 no data about sex Age 56.1 ± 7.5 n~=59	Groups 1.CON n= 19 2.HP n= 21 3.CON+RT n = 22 4.HP+ RT n=20 Intervention length 16 months Mode group face to face Follow up nil	all groups isocaloric, energy-restricted diet CON; carbohydrate: protein: fat (53:19:26) HP; 43:33:22	Parallel study groups: 1.CON energy restricted standard carbohydrate low-protein, low-fat diet alone 2. CON +RT 3.HP isocaloric higher-protein, moderate –carbohydrate, low- fat alone 4.HP+ RT RT: (progressive resistance training with eight separate exercises for 16 week
Author Praet S. F. E. 2008 The Netherlands (21)	RCT Diabetologia (2008)	T2DM n* =92 no data about sex Age 60±9 n~ = 37	Groups 1.brisk walking n= 49 2)medical fitness programme n=43 Intervention length 12 months Mode: group face to face and individual face to face Follow up 12 months	consultation with dietitian or diabetes nurse dietary guidance	**brisk walking** "three 60 min exercise sessions participants were supervised during the first three months 15 and 25 patients in one group **endurance exercise training**:5–6 km/h brisk walking, the intensity increased and averaged 75±5% of maximum heart frequency **medical fitness programme**: Endurance type exercise of interval type exercise on a home trainer three time at week The resistance type exercise training consisted of resistance and floor exercises using individual body weight and/or elastic band" (21). After 6 months 80 to 225 min per week

Table 2. Characteristic of Included Studies (continued)

Author, year and study name Country	Design journal name	Participants	Intervention groups (n) Intervention length Follow up	Description of dietary intervention	Description of physical activity intervention
Di Loreto C. et al. 2004 Italy (22)	randomised post hoc analysis, retrospective analyse Diabetes Care (2005)	T2DM n* =182 no data about sex Age 62±1 n~ = 179	Groups 1. group 0 (no activity, n =28), group 1–10 (6.8 ±0.3 METs /h/week, n = 27), group 11–20 (17.1±0.4, n=31), group 21–30 (27.0 ±0.5, n =27), group 31– 40 (37.5 ± 0.5, n = 32),and group >40 (58.3 ±1.8, n= 34), including all the subjects who achieved change in energy expenditure >40 METs/ h/ week. Follow up: 2 years	all patients become recommendation for diet : 55% of calories from complex carbohydrates, 30% from fat, and 15% from protein. A negative balance diet (~300 kcal/day) was recommended to overweight and obese participants voluntary physical activity was included in the calculation of energy expenditure	it was observed and analysed what are the "long-term effects of increased energy expenditure through voluntary aerobic physical activity Participants were followed for 2 years. It were six groups based on their increments in METs per hour per week" (22)
Ligtenberg P.C. Hoekstra J.B.L. Bol L E. Zonderland M.L. Erkelen D.W. 1997 The Niederlands (24)	Randomised prospective study Clinical science (London, England : (1997)	T2DM n* = 58 M: 20 F: 38 Age : mean 62±5; range 55-75 years	Groups TG: three sessions a week exercises of major muscle groups Phase 1: 6 week group training under direct supervision, Phase 2: 6 week training at home individually (contact once over two weeks) Phase 3: training at home No contact by the investigator CG: the control group had only one educational program Follow up: nil	not reported	three sessions a week exercises of major muscle groups bicycle ergometer, swimming, treadmill, rowing etc. 50min,three times in a week supervised period during 12 week non-supervised period during 14 week

SD – standard deviation; INT –intervention group; CG control group ;ES- enhanced strength training program ; SST- standard strength training program; ILI – intensive lifestyle intervention, DSE-diabetes support and education, DPP-diabetes prevention programme; CON-carbohydrate: protein: fat ; HP-high protein; RT resistance training; MET – metabolic equivalents

Table 3. Results of Included Studies (continued at the next pages)

Author Year Name(SN)	Analysis	Outcome measures	Results for diabetes markers and weight	Results on dietary and exercise outcomes	Retention
Author **Simpson** **et al.** **2015** **(SN) GREAT2DO** (19)	linear mixed models for ITT analysis was used to observe the differences between groups Bonferroni corrections, Hedges' bias-corrected ES for small sample sizes and interpreted according to Cohen's interpretation of "trivial" (<0.20), "small" (≥0.20 < 0.50), "moderate" (≥0.50 < 0.80), and "large" (≥0.80) ES was used as statistical assessment	Primary outcome: -insulin resistance 96 hours after the last exercise (HOMA2 IR) -HbA1c Secondary outcome: BMI, Bia and CV health parameter	Mean change after 12 months Power training group vs. shame exercise group ↓ HOMA 2IR -0.6 HbA1c (mmol/mol) -13.1	not reported	35/108 (34%) completed the 6 year follow up; remaining 6 participants scheduled for final assessment
Autor **Teychenne M. et al.** **2015** **(SN)** **STRONG** (23)	"SPSS software version 19.0 Stata statistical software release 12.0 Analyses were undertaken for the pooled sample and separately for those with and without T2DM."(23)	-HbA1c, -upper and lower body muscle strength, - weight, -LTPA (leisure-time-physical activity)	**Group :T2DM/EST**: it was a significant reduction in HbA1c after six months and one year **Group without T2DM** : it was no differences in HbA1c during through a year **Weight and BMI:** similar results in both groups after sex months **(**adoption phase), after one year significant better results in the EST group	**Changes in muscle strength and LTPA (leisure-time-physical activity)** "significant increase in upper and lower body strength and LTPA within the both group for participants both with and without T2DM. no significant between group changes from baseline were observed in upper body strength, lower body strength and LTPA during the adoption or the maintenance phase for participants with T2DM and participants without T2DM**"** (23)	47/127 (15%) completed 12 Months

Table 3. Results of Included Studies (continued)

Author, Year Name(SN)	Analysis	Outcome measures	Results for diabetes markers and weight	Results on dietary and exercise outcomes	Retention
The Look AHEAD Research Group (10,25,30)	Means reported at baseline are unadjusted averages. The mixed effects maximum likelihood and GEE analysis of repeated outcomes was carried out in Proc Mixed of SAS, Version 9, using a 0.05 alpha level.	-Hba1c -Body weight -Physical Fitness -Systolic blood pressure -Waist circumference	the greatest benefits were often seen at 1 year Cardiovascular events were not significant reduced with a lifestyle intervention and weight loss in adults with type 2 diabetes and overweight or obese after a period of four years	"cardiovascular morbidity and mortality in persons with type 2 diabetes can be significant reduced through an intensive lifestyle intervention with dietary program , exercise and weight loss at the first four years " (10,25,30)	5016/5145 (97%) completed 11 year
Author Wycherley T.P. at al. 2010 (20)	SPSS for Windows (version 17.0) one-way ANOVA for continuous variables and 2 tests for categorical variables. "Changes over time in the groups were assessed using repeated-measures ANOVA."(20)	-body weight and composition -HbA1c -blood pressure -serum insulin -triglycerides -total cholesterol -HDL, LDL -CRP -Creatinine clearance	**Between group differences at 16 week** **CON : week0/week16** BW (kg) -8.6 ± 4.6 (-8.9%) HbA1c(%) -1.1 ± 0.6 **HP : week0/week16** BW (kg) -9.0 ± 4.8 (- 8.7%) HbA1c (%) -1.8 ± 1.6 **CON+RT week0/week16** BW (kg) -10.5 ±5.1 (-10.0%) HbA1c (%) -1.1 ±0.7 **HP+RT week0/week16** BW (kg) -13.8 ±6.0 (-12.7%) HbA1c (%) -1.1 ±0.7	not reported	59/83 (71%) completed 16 months

Table 3. Results of Included Studies (continued)

Author,Year Name(SN)	Analysis	Outcome measures	Results for diabetes markers and weight	Results on dietary and exercise outcomes	Retention
Author Praet S. F. E. 2008 (21)	ANOVA repeated Unpaired Student's t, χ2 and Mann–Whitney U tests measures, was used Significance was set at the 0.05 level of confidence. "Pearson's correlation calculation was used to test for linear relationships between long-term changes in dependent variables. All statistical calculations were performed using SPSS 10.1 (SPSS, Chicago, IL,USA)"(21)	HbA1c BMI Fasting plasma glucose HOMA Resting heart rate blood pressure syst/ dyast) cholesterol LDL/HDL Triglyceride	-changes in HbA1c values were identical in both groups (95% CI −0.42, 0.43;p=0.99) excluded the participants those had be prescribed higher doses of blood glucose-lowering medication through the follow –up period , HbA1c increased by 0.05% (95% CI −0.41, 0.51; p=0.82) in brisk walking as compared with medical fitness programme. -BMI did not change	not reported	27/92 (29%) completed 12 months

Table 3. Results of Included Studies (continued)

Author,Year Name(SN)	Analysis	Outcome measures	Results for diabetes markers and weight	Results on dietary and exercise outcomes	Retention
Author Di Loreto C. et al 2004 (22)	"SE and 95% CI, paired samples *t* tests, linear regressions according to the least-squares method was used to calculate average rate of change for each variable"(22)	10 year CHD Risk body weight/BMI waist circumference FPG/Hba1c blood pressure heart rate cholesterol; HDL, LDL triglycerides	**Group 0** "no significant change in any of the parameters, except for a significant increase (*P*<0.01) in medical costs (drugs)" (22) **Group 1–10** "no significant change in any of the health parameters examined and no significant change in medical or indirect social costs after 2 years" (22) **Group 11–20** "significant reductions in HbA1c (*P* < 0.0001), systolic (*P* =0.0286) and diastolic (*P* = 0.003) blood pressure, total cholesterol (*P* < 0.0001), triglycerides (*P* < 0.0001), and 10-year CHD risk (*P* = 0.0003)" (22) **Group 21–30** "significant (*P* < 0.0001) reductions in body weight, BMI, waist circumference ,FPG, HbA1c, systolic (*P* =0.048) and diastolic (0.0156) blood pressure, heart rate, total and LDL (*P* =0.0229) cholesterol, and triglycerides; an ~4% reduction in 10-year CHD risk; and a significant (*P*<0.0001) increase in HDL cholesterol" (22) **Groups 31–40 and >40** "significant (*P*<0.0001) reductions in body weight, BMI, waist circumference, FPG, HbA1c, systolic and diastolic blood pressure, heart rate, total and LDL (*P* = 0.012) cholesterol, and triglycerides; a 4–5% reduction in 10- year CHD risk; and a significant (*P* <0.0001) increase in HDL cholesterol" (22)	Retrospective analyse no data about dietary and exercise outcome	179/182 (98%) completed 2 years

Table 3. Results of Included Studies (continued)

Author,Year Name(SN)	Analysis	Outcome measures	Results for diabetes markers and weight	Results on dietary and exercise outcomes	Retention
Ligtenberg P.C. Hoekstra J.B.L. Bol L E. Zonderland M.L. Erkelen D.W. (24)	"Multivariate analysis of variance (MANOVA), with repeated measures design, was used to test differences within (time) and between groups. *P* < 0.05 was considered to be significant" (24)	HbA1c fasting C-Peptide total cholesterol VLDL cholesterol HDL cholesterol triglycerides apolipoprotein A+B body weight	unchanged fasting blood glucose level in both groups during the study. no significant changes in HbA1c level between groups after 6 or 26 weeks of training it was a significant differences between previous more active and previous less active patients in HbA1c levels: 8.6 ±1.2% and 9.1 ± 1.3% . the difference increased after 6 weeks of training:8.4 ± 1.5% and 9.5± 2.1% *(*P **≤** 0.05) respectively it was no changes on insulin sensitivity and C-peptide values	"body weight did not change in either group during the whole study period the total energy intake between the training group and the control group was significantly different after 6 weeks of training [training group: 7.95 ±3.0 kJ (prestudy) and8.27 ± 1.7 kJ (after 6 weeks) compared with control group: 7.17 ±1.7 (prestudy) and 6.66 ±1.8 (after6 weeks);P≤10.011. Significant changes were found between groups concerning the intake of protein [training group: 80.5 f27.5 g/day (prestudy) and 81.6±17 g/day (after 6 weeks) compared with control group: 72 ±16.5 g/day (prestudy) and 66.0 **±**19.6 g/day (after 6 weeks); P≤0.01l], and carbohydrates [training group: 180.3 ±70 g/day (prestudy) and 187.3 ±52.2 g/day (after 6 weeks) compared with control group: 167.2 ±50.5 g/day (prestudy) and 153.5 ±59.3 g/day (after 6 weeks); P≤0.051" (24)	51/58 (88%) completed 26 weeks

6. DISCUSSION

6.1. Summary of evidence

To summarise all results from seven described studies, with or without quantitative data, was on the one hand clear and easy because of evidences of benefits of exercise and physical activity in all studies. On the other hand there were many differences and heterogeneities of studies at operational, conceptual, design and statistical levels. The number of participants was varied in all studies, a difference of between 58 and 5145 was described. A different duration- and follow-up time were also described. The shortest study duration was sixteen weeks and the largest and longest follow up was interrupted after eleven years. The eligibility criteria in all studies were that the participants had diagnosed type 2 diabetes, were previously physical inactive and the data from baseline showed in all studies overweight or obesity. The important metabolic parameters were measured on the baseline and then in each study with a different assessment schedule (10,19–24).The goal of the review author was to establish the effect of physical activity in structured exercise programs (with or without dietary component) on blood sugar control in type 2 diabetes. One of the seven studies reporting about effects of physical activity in type 2 diabetes, was a retrospective /post hoc analysis and one study was a multi-centre randomised trial (16 centres in the U.S.) There were distinct variations in the description of physical activity and poor reporting about nutritional intervention and results. The short-term studies of life style intervention included physical activity and diet, showing many benefits and improvements relating to glycemic control and diabetes-related coexisting illness.

The benefit of exercise and life style change is evident in all studies that compared sedentary participants and the active participants group. Primary outcome in all seven studies was the change in glycaemia. All studies measured HbA1c and some of them also measured fasting plasma glucose, serum insulin and/or insulin sensitivity used HOMA2 IR (19–21). The medication at the baseline was describe in all studies but the changes in the doses of medication were not. Smoking habits

were verifeid in four studies. As known smoking deserves to be taken into account of the risk factors of cardiovascular diseases.
The most important approach in type 2 diabetes therapy is to stop the developing of disease and of macrovascular and microvascular complications that make the most chronical complications and cause high social and medical costs. One of seven studies reported about consequences on both of them (38). Brisk walking studies described the non-inferiority of brisk walking compared with medical fitness program, on cardiovascular parameter.

All studies included in the review described several cardiovascular health parameters at the baseline and also at the relevant time points of the study (10,19–24).The largest and the study with the highest number of participants was “The Look AHEAD” study, which compared the effect of an intensive lifestyle intervention with a control group of participants who attend standard diabetes education. It was found that overweight or obese adults with type 2 diabetes can lose weight with intensive multicomponent lifestyle intervention. It was observed that maximal weight loss took place in the first year and modest weight loss was maintained during a ten-year period. Weight loss and improved fitness were significantly assessed mediators. The intervention group had a relative reduction of 48% in the danger of loss of mobility. Greater reduction in all cardiovascular risk factors, in exception of low-density-lipoprotein, was observed (10,33,39).How the course changed after four years is shown in Figure 5.

I did not find many studies with synchronous implementation of exercise and validated nutritional programs. However a comparison of one of the studies in this review showed the influence of a high protein versus standard carbohydrate diet, with or without assisted resistance exercise and showed substantial advancement in cardiovascular risk factors and glycemic control following lifestyle intervention. This study included a structured, energy-restricted diet that occurred independent of macronutrient composition or participation in a resistance training program. The participants were obese adults with type 2 diabetes and sedentary lifestyle. As a result of additional resistance training an increased weight and fat mass loss were observed. Furthermore it was shown that, this effect magnified by replacing some

dietary carbohydrates with protein (20). We know that participants adoption and maintenance is a major challenge in training programs .One study compared the effectiveness of standard strength training programs to an enhanced training program (23). A behaviourally-focused enhanced strength program intervention showed better results for the adoption of strength training in the adults with overweight. The improvements in glycemic control in adults with type 2 diabetes were described.

The lifestyle intervention is a causal therapy, and has to be explained and advocated by a medical practitioner. To communicate the message high motivation and implementation effort are essential. The diabetes education teams with diabetes nurse, nutritional specialist and physician with diabetes knowledge are an essential support advice for type 2 diabetes patients. In agreement with the conclusions of this review, the physio therapist or sport physician should be involved in the team.

6.2. Limitations

This systematic review did not include a meta-analysis because of the heterogeneity of studies. There was only one author of a systematic review which means the possibility of a subjective interpretation of results. Because of the short duration of some trials, there is no report of significant long term complications or mortality. A small number of participants was included in the analyses for quality of life and social cost.

7. CONCLUSIONS

The basic therapeutic tool that supports drug and insulin therapy in adults with type 2 diabetes is to increase physical activity and to follow dietary advice. “Exercise is the real polypill”(40) is the name of a title which explain all the benefits of physical activity and there importance for a healthy life. Physical activity is the best medicine, free and does not have any side-effects. Although the available education and

training programs try to communicate importance of changing one´s lifestyle as a milestone of type 2 diabetes therapy. Type 2 diabetes prevalence is one of the most medically worrying topics. That is the reason for many studies that have investigated the influence of systematically increased physical activity and have tried to describe the best combination of a dietary, behavioural and physical activity program for type 2 diabetes. The World Health Organisation recommends in the Global Report on Diabetes 2016: “Multisector, population-based approaches are needed to reduce the prevalence of modifiable diabetes risk factors – such as overweight, obesity, physical inactivity and unhealthy diet – in the general population” (2). “It is recommended that adults aged 18–64 years should do at least 150 minutes of moderate-intensity aerobic physical activity (for example brisk walking, jogging, gardening) spread throughout the week, or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity” (2). The seven studies in this review had differences in the choice of the kind of physical activity, in the number of participants, in the dietary program, in the statistics, but all of them recognised that a well ordered movement program plays a big role and is a support to drug and insulin therapy for type 2 diabetes. Physical activity has a very important part in the therapy of type 2 diabetes. Physical activity together with dietary interventions and instructions make a basic step in the diabetes education and lead to better glycemic control and better quality of life without the many difficult complications of type 2 diabetes.

8. CONFLICT OF INTEREST

The Author has no conflict of interest to disclose.

As a quote at the end the number one lesson from François Lelord´s “Hector and the search for happiness”:

Making comparisons can spoil your happiness

But ……I did, and it made me happy

10. REFERENCES

1. American diabetes association. Diagnosis and classification of diabetes mellitus. Diabetes Care [Internet]. 2013;36 Suppl 1(Supplement 1):S67-74. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3006051&tool=pmcentrez&rendertype=abstract%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/9118500%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/22187472%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=

2. World Health Organization. Global Report on Diabetes [Internet]. ISBN. 2016. Available from: http://www.who.int/about/licensing/%5Cnhttp://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

3. International Diabetes Federation. IDF Diabetes Atlas - Seventh Edition. Int Diabetes Fed [Internet]. 2015; Available from: http://www.diabetesatlas.org/

4. International Diabetes Federation (IDF). IDF Diabetes Atlas 7th edition [Internet]. idf.org. 2015. Available from: http://www.diabetesatlas.org/

5. Wild Sarah, Roglic Gojka, Green Anders, Sicree Richard, Hilary K. Global Prevalence of Diabetes: Estimates for the year 2000 and projection for 2030. Diabetes Care. 2004;27(5):1047–53.

6. Connolly V, Unwin N, Sherriff P, Bilous R, Kelly W. Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. J Epidemiol Community Health. 2000;54(3):173–7.

7. Klein S, Sheard NF, Pi-Sunyer X, Daly AE, Wylie-Rosett J, Kulkarni KD, et al. Weight Management Through Lifestyle Modification for the Prevention and Management of Type 2 Diabetes: Rationale and Strategies. Diabetes Care [Internet]. 2004;27(8):2067–73. Available from: http://care.diabetesjournals.org/content/27/8/2067.short

8. Cameron F. Standards of Medical Care in Diabetes - 2016. Aust Fam physician. 2006;35(6):386–90.

9. Rossen J, Yngve A, Hagströmer M, Brismar K, Ainsworth BE, Iskull C, et al. Physical activity promotion in the primary care setting in pre- and type 2 diabetes - the Sophia step study, an RCT. BMC Public Health [Internet]. 2015;15(1):647. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84936886208&partnerID=tZOtx3y1

10. Group LAR, Bray G, Gregg E, Haffner S, Pi-Sunyer XF, WagenKnecht LE, et al. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. Diab Vasc Dis Res. 2006;3(3):202–15.

11. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29(9):2102–7.

12. Reusch JEB, Bridenstine M, Regensteiner JG. Type 2 diabetes mellitus and exercise impairment. Rev Endocr Metab Disord [Internet]. 2013;14(1):77–86. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3593997&tool=pmcentrez&rendertype=abstract

13. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. A Randomized Controlled Trial of Resistance Exercise Training to Improve Glycemic Control in Older Adults With Type 2 Diabetes. Diabetes Care. 2002;25(12):2335–41.

14. Aguiar E, Morgan P, Collins C, Plotnikoff R, Callister R. The effectiveness of multi-component Type 2 Diabetes prevention programs including diet, aerobic exercise and resistance training: A systematic review and meta-analyses. Obes Res Clin Pract [Internet]. 2012;6:79. Available from:

http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70899241%5Cnhttp://dx.doi.org/10.1016/j.orcp.2012.08.162

15. Nield L, Moore H, Hooper L, Cruickshank K, Vyas A, Whittaker V, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults (Review). Cochrane Database Syst Rev [Internet]. 2007;1(1):1–89. Available from: http://doi.wiley.com/10.1002/14651858.CD004097.pub4%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/17636747%5Cnhttp://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004097.pub4/pdf/standard

16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Ioannidis JP a, Clarke M, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions : Ann Intern Med. 2009;151(4):W65–94.

17. Boudin F, Nie J, Dawes M. Clinical Information Retrieval using Document and PICO Structure. Annu Conf North Am Chapter Assoc Comput Linguist. 2010;(June):822–30.

18. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement : Updated Guidelines for Reporting Parallel Group Randomized Trials TO CONSORT. Ann Intern Med Acad Clin [Internet]. 2010;152(11):1–8. Available from: http://dx.doi.org/10.1016/j.jclinepi.2010.02.005%5Cnwww.annals.org

19. Simpson KA, Mavros Y, Kay S, Meiklejohn J, de Vos N, Wang Y, et al. Graded Resistance Exercise And Type 2 Diabetes in Older adults (The GREAT2DO study): methods and baseline cohort characteristics of a randomized controlled trial. Int J Behav Nutr Phys Act. England; 2015 Aug;12:512.

20. Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. A High Protein Diet With Resistance Exercise Training Improves Weight Loss And Body Composition In Overweight And Obese Patients With Type 2 Diabetes. Diabetes Care [Internet]. 2010; Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20150293

21. Praet SFE, Van Rooij ESJ, Wijtvliet A, Boonman-De Winter LJM, Enneking T, Kuipers H, et al. Brisk walking compared with an individualised medical fitness programme for patients with type 2 diabetes: A randomised controlled trial. Diabetologia. 2008;51(5):736–46.

22. Di Loreto C, Fanelli C, Lucidi P, Murdolo G, De Cicco A, Parlanti N, et al. Make your diabetic patients walk: Long-term impact of different amounts of physical activity on type 2 diabetes. Diabetes Care. 2005;28(6):1295–302.

23. Teychenne M, Ball K, Salmon J, Daly RM, Crawford DA, Sethi P, et al. Adoption and maintenance of gym-based strength training in the community setting in adults with excess weight or type 2 diabetes: a randomized controlled trial. Int J Behav Nutr Phys Act. England; 2015 Aug;12:105.

24. Ligtenberg PC, Hoekstra JB, Bol E, Zonderland ML, Erkelens DW. Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients [Internet]. Clinical science (London, England : 1979). 1997. p. 127–35. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/633/CN-00143633/frame.html

25. Wesche-Thobaben J, Mancino J, Jackson S, Kitabchi A, Hodges M, Montgomery B, et al. The development and description of the comparison group in the Look AHEAD trial. Clin Trials. 2011;8(3):320–9.

26. Roden M. Exercise in type 2 diabetes: To resist or to endure? Diabetologia. 2012. p. 1235–9.

27. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med

[Internet]. 2001;161(13):1581–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11434789

28. Minges KE, Cormick G, Unglik E, Dunstan DW. Evaluation of a resistance training program for adults with or at risk of developing diabetes: an effectiveness study in a community setting. Int J Behav Nutr Phys Act. 2011;8.

29. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Med Sci Sports Exerc. 2001;33(7):1126–41.

30. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med [Internet]. 2010;170(17):1566–75. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2010.334%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/20876408%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3084497

31. Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, Williamson D, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity (Silver Spring). 2006;14(5):737–52.

32. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: New developments in diet, physical activity, and behavior therapy. Circulation. 2012. p. 1157–70.

33. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med [Internet]. 2013;369. Available from: http://dx.doi.org/10.1056/NEJMoa1212914

34. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA - J Am Med Assoc. 2012;308(23).

35. Phelan S, Kanaya AM, Subak LL, Hogan PE, Espeland MA, Wing RR, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. J Urol [Internet]. 2012;187(3):939–44. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3646565&tool=pmcentrez&rendertype=abstract

36. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med. 2009;169(17):1619–26.

37. Faulconbridge LF, Wadden TA, Rubin RR, Wing RR, Walkup MP, Fabricatore AN, et al. One-Year Changes in Symptoms of Depression and Weight in Overweight/Obese Individuals with Type 2 Diabetes in the Look AHEAD study. Obesity (Silver Spring) [Internet]. 2012;20(4):783–93. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298842/

38. Di Loreto C, Fanelli C, Lucidi P, Murdolo G, De Cicco A, Parlanti N, et al. Make Your Diabetic Patients Walk. Diabetes Care [Internet]. 2005;28(6):1295–302. Available from: http://care.diabetesjournals.org/content/28/6/1295.abstract

39. Rejeski WJ, Ip EH, Bertoni AG, Bray GA, Evans G, Gregg EW, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. N Engl J Med [Internet]. 2012;366(13):1209–17. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1110294%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012180295%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/22455415%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC333903

40. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiol [Internet]. 2013;28(5):330–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23997192