New Diabetes Guidelines

Your doctor ~~may~~ will not tell you

INDO-VIETNAM
MEDICAL BOARD

Dr. Biswaroop Roy Chowdhury

New Diabetes Guidelines

Your doctor ~~may~~ *will* not tell you

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DEDICATION

Dedicated to my angel daughter Ivy,

loving wife Neerja

&

caring parents

Shri Bikash Roy Chowdhury

Shrimati Lila Roy Chowdhury.

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  Author : Dr. Biswaroop Roy Chowdhury

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SECTION - 1

- **Your Doctor Will Not Tell You**

- **Plain Language Interpretation of New Diabetes Guidelines**

YOUR DOCTOR WILL NOT TELL YOU

For the first time in the history of medical science, there is a good news for the Diabetes Patients i.e. the New Diabetes Guidelines, which were released by the ACP (American College of Physicians) on 6th March 2018 (published in Ann Intern Med. doi:10.7326/M17-0939). Those who are familiar with my research work in the field of diabetes will know that I have been warning and elucidating the masses through my training programs, You-tube videos and especially through my book "Last days of Diabetes" about the following cover up truth :-

1) If you are able to maintain an average blood sugar less than or equal to 250 mg/dl (14 mmol/lt) without the interference of medicine; then you are not a diabetic patient.

2) Trying to control blood sugar with medication/insulin may give you desirable blood sugar number but at the cost of making you more sick and increasing the chances of death.

The new diabetes guidelines are very much in line with the above two statements. Certainly, your doctor will never tell you about the new guidelines because by adopting the new guidelines, 70% of the previously diagnosed diabetes patients will automatically convert into non-diabetic. A huge loss of business for the profit minded doctors!

The section 1 of the book attempts to explain the 4 Guidance Statements released by the ACP in plain language, so that the patients can understand and make necessary changes in their medications accordingly. Section 2 covers the full text of the new diabetes guidelines as is published in Annals of Internal Medicine.

As a major relief to the diabetes patients, they can now eat as much fruits as they want, especially the sweet fruits like mango & jack fruits. As is known to my patients, I have been promoting "fruits for diabetes cure" since 2013, especially through my book "Diabetes Type I and II Cure in 72 Hours"; it's only in December 2017, when this is proved to be true by the mainstream medical science.

The 3rd section of the book covers the full text of the research paper on "Influence of fruit on glycemic control" as is published in the Journal of Nutritional Science (publisher - Cambridge University Press) dated 15th December 2017.

The 4th section of the book is the full text of my own research paper which was published prior to the above two papers (on October 24,2017), in the Journal of Metabolic Syndrome with DOI number http://dx.doi.org/10.4172/2167-0943-C1-005

It's a sigh of relief that the mainstream medical science has corrected the protocol for Diabetes patients, but sadly the modern doctors decided not to pass on this extremely important and beneficial knowledge to their diabetic patients as it may mean contradicting their own preachings and recommendations which they were practicing for many decades.

PLAIN LANGUAGE INTERPRETATION OF NEW DIABETES GUIDELINES

Based on ACP (American College of Physicians) Clinical Guidelines, published in Annals of Internal Medicine on 6th March 2018 :-

Guidance Statement 1 :

Guidance Statement 1: *Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*

Interpretation : The above guidelines are based on the famous Accord Trial (see the box below),

ACCORD Trial

HbA1C < 6%	HbA1C < 8%
Blood Sugar < 150mg/dl <8.3mmol/lt	< 228mg/dl <12.7mmol/lt
• 22% more death • 36% more cardiovascular related death • Increased weight by 10kg • Increased fluid retention	

where it was seen that trying to control blood sugar with medication may result in lowering of blood sugar and achieving a target of HbA_{1c} below 6% but at the cost of at least 22% increase in chances of death. So, the new Diabetes Guidelines discourage the practitioners from using medication to control blood sugar.

The take home message is high blood sugar (i.e. greater that 250 mg/dl or 14 mmol/lt) is bad but trying to lower the blood sugar with medication is worse.

Guidance Statement 2 :

Guidance Statement 2: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*

The Guideline statement 2 is based on the results of UKPDS Trails and VADT (Veteran's Affair Diabetes Trail) where it was seen that, maintaining the HbA_{1c} target near to 8% and 8.4% respectively is much beneficial for the patients in comparison to trying to achieve a target of HbA1c less than 6%.

For daily monitoring to achieve the above goal of HbA1c, you may convert the HbA_{1c} target (i.e. 8.4%) to mg/dl or mmol/lt using the below given formula.

Diabetes Control & Complications Trial (DCCT)

Average Blood Glucose

mg/dl = (35.6 x HbA1c)* – 77.3

mmol/lt = (1.98 x HbA1c)* – 4.29

*** Add 10% for capillary blood sample**

New England Journal of Medicine - 1993

(35.6 x 8.4) -77= 222mg/dl

(1.98 x 8.4) - 4.29 = 12.35 mmol/lt

This mean if every day on an average you are able to maintain a blood sugar near 222mg/dl or 12.35mmol/lt, then it translates to achieving an HbA_{1c} equal to 8.4%.

This blood sugar value (222mg/dl) is with the assumption that you take the blood sample from the vein. However, at home setting while using the standard Glucometer, you take the blood sample from capillary (finger tip).The capillary blood on an average shows blood sugar up to 10% more than the blood sample from vein, so at home setting the target blood sugar should be less than or equal to

222+ 10 % = 244 mg/dl

12.34+ 10 % = 13.5mmol/lt

Guidance Statement 3 :

Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

Interpretation : Using the above formula, HbA1c of 6.5% translates to 170mg/dl or 9.4mmol/lt. This means while on diabetes medication/insulin, if your average blood sugar drops below 170mg/dl or 9.4mmol/lt, then you need to taper down the medication/insulin.

Guidance Statement 4 :

Guidance Statement 4: *Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*

Interpretation: The guideline 4 is based on VADT (as shown in the table below):

VADT Trial	
HbA1C ≤ 6.9%	≤ 8.4%
Blood Sugar ≤ 185mg/dl ≤10mmol/lt	≤ 244 mg/dl ≤ 13.5mmol/lt
• More hypoglycemic • 3 times higher impaired consciousness • More breathing problem	

In VADT, it was seen that trying to control the blood sugar levels with medication/insulin among the patients older than 60 yrs and especially with chronic conditions like heart diseases, COPD , cancer and dementia, led to increased risk of death and other adverse affects. So, for patients older than 60 yrs, medication/insulin should be given only, if it leads to symptomatic relief like reduction in abnormally high frequency of urination, lessening of fatigue etc.

SECTION - 2

Clinical Guideline

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For author affiliations, see end of text.

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ACP American College of Physicians℠
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CLINICAL GUIDELINE

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Devan Kansagara, MD, MCR; Carrie Horwitch, MD, MPH; Michael J. Barry, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians developed this guidance statement to guide clinicians in selecting targets for pharmacologic treatment of type 2 diabetes.

Methods: The National Guideline Clearinghouse and the Guidelines International Network library were searched (May 2017) for national guidelines, published in English, that addressed hemoglobin A_{1c} (HbA_{1c}) targets for treating type 2 diabetes in nonpregnant outpatient adults. The authors identified guidelines from the National Institute for Health and Care Excellence and the Institute for Clinical Systems Improvement. In addition, 4 commonly used guidelines were reviewed, from the American Association of Clinical Endocrinologists and American College of Endocrinology, the American Diabetes Association, the Scottish Intercollegiate Guidelines Network, and the U.S. Department of Veterans Affairs and Department of Defense. The AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument was used to evaluate the guidelines.

Guidance Statement 1: *Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*

Guidance Statement 2: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*

Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

Guidance Statement 4: *Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*

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Diabetes mellitus is a leading cause of death in the United States and is associated with microvascular and macrovascular complications. Approximately 29.1 million persons, or 9.3% of the U.S. population, have type 2 diabetes (1). In 2012, the total direct and indirect costs associated with diabetes in the United States were $245 billion (1). Markedly elevated glucose levels can result in subacute symptoms, such as polyuria, polydipsia, weight loss, and dehydration. Over time, the metabolic derangements associated with diabetes may lead to vision loss, painful neuropathy or sensory loss, foot ulcers, amputations, myocardial infarctions, strokes, and end-stage renal disease. Lowering blood glucose may decrease risk for complications, but lowering strategies come with harms, patient burden, and costs.

Blood glucose can be measured in various ways, including the hemoglobin A_{1c} (HbA_{1c}; also called glycosylated or glycated hemoglobin) level, which approximates average blood glucose control over about 3 months. As with all laboratory tests, HbA_{1c} measurements are associated with variability (2) and can vary further with race and ethnicity (3–5). Guidelines have historically recommended initiation or intensification of

See also:

Summary for Patients 2

Web-Only
CME/MOC activity

* This paper, authored by Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Devan Kansagara, MD, MCR; Carrie Horwitch, MD, MPH; Michael J. Barry, MD; and Mary Ann Forciea, MD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Mary Ann Forciea, MD† (Chair); Nick Fitterman, MD†; Kate Balzer, MSW†§; Michael J. Barry, MD†; Cynthia Boyd, MD, MPH†; Carrie Horwitch, MD, MPH†; Linda L. Humphrey, MD, MPH†; Alfonso Iorio, MD, PhD†; Devan Kansagara, MD, MCR†; Jennifer Lin, MD, MCR†; Scott Manaker, MD, PhD‡; Michael Maroto, JD, MBA†§; Robert McLean, MD†; Reem Mustafa, MD, PhD, MPH†; Janice Tufte†§; Sandeep Vijan, MD, MS‡; and Timothy J. Wilt, MD, MPH†. Approved by the ACP Board of Regents on 26 March 2017.
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§ Nonclinician public representative.

pharmacologic therapy to achieve specific HbA_{1c} targets, depending on the population in question. The ideal target that optimally balances benefits and harms remains uncertain.

GUIDANCE STATEMENT FOCUS AND TARGET POPULATION

The purpose of this American College of Physicians (ACP) guidance statement is to critically review the available guidelines from various organizations and the evidence included therein to assist clinicians in making decisions about targets when using pharmacologic therapy in adults with type 2 diabetes. Recent data suggesting that newer agents reduce cardiovascular morbidity and mortality in high-risk patients with type 2 diabetes have prompted calls for a fundamental shift in diabetes management. Some anticipate that treatment decisions will eventually be based more on cardiovascular risk than achievement of specific HbA_{1c} targets, analogous to recent changes in lipid management. However, for the foreseeable future, glycemic targets will continue to influence management decisions by front-line clinicians (6). This statement focuses on the benefits and harms of targeting lower versus higher HbA_{1c} levels and does not cover use of specific medications outside of their use to achieve HbA_{1c} targets. The intended audience is all clinicians, and the target population is nonpregnant adults with type 2 diabetes.

METHODS

The Clinical Guidelines Committee (CGC) of ACP develops guidance statements on topics where several conflicting guidelines are available. We provide clinicians with a rigorous review of the guidelines and the evidence they include. We then adopt the clinical recommendations if we agree with their evaluation of benefits and harms or adapt them if changes are needed based on our assessment of the recommendations and evidence.

Data Sources and Guideline Selection

We searched the National Guideline Clearinghouse and the Guidelines International Network library (May 2017) for guidelines on recommended HbA_{1c} targets in the treatment of type 2 diabetes in nonpregnant outpatient adults. We included guidelines that were developed by national organizations, were published in English, and targeted the correct population. We reviewed titles and abstracts and excluded guidelines that were modified or adapted from other organizations or addressed specific populations (such as pregnant women or patients with kidney disease). Our search yielded guidelines from the National Institute for Health and Care Excellence (NICE) (7) and the Institute for Clinical Systems Improvement (ICSI) (8). On the basis of the knowledge and expertise of ACP CGC members, we also selected the following 4 guidelines not identified in either database at the time of the search but commonly used in clinical practice: the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guideline (9), the American Diabetes Association (ADA) guideline (10), the Scottish Intercollegiate Guidelines Network (SIGN) guideline (11), and the U.S. Department of Veterans Affairs and Department of Defense (VA/DoD) guideline (12).

Quality Assessment

Six coauthors independently reviewed and assessed each guideline using the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument (13). This instrument asks 23 questions in the following 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The authors scored each guideline independently, and the scores were compared (**Appendix Figure** and **Appendix Table 1**, available at Annals.org). Authors then provided a summary determination of whether they "would recommend this guideline for use" by recording "yes," "no," or "yes with modifications."

Peer Review

The draft guidance statement was peer-reviewed through *Annals of Internal Medicine* and was posted online for comments from ACP Regents and Governors, who represent ACP members at the regional level. The final guidance statement incorporated comments from peer reviewers and ACP Regents and Governors.

Public Panel Review

The development of this guidance statement also included perspectives, values, and preferences of 2 CGC members who represent the public and a 7-member public panel.

SUMMARY OF EVALUATED GUIDELINES USING THE AGREE II INSTRUMENT

We reviewed and rated 6 guidelines (AACE/ACE [9], ADA [10], ICSI [8], NICE [7], SIGN [11], and VA/DoD [12]), focusing solely on sections addressing HbA_{1c} targets in patients with type 2 diabetes. **Appendix Table 1** shows the detailed scaled domain scores and average quality ratings for each guideline, and the **Appendix Figure** shows average AGREE II scores for each item in each of the 6 domains. The fundamental difference between high- and low-scoring guidelines was methodology. The 2 lowest-scoring guidelines, AACE/ACE and ADA, scored lowest on stakeholder involvement, applicability, editorial independence, and scientific rigor. A systematic review is the backbone for any trustworthy guideline, but some guidelines might not be based on a systematic review or may not have made the review publicly available (14, 15).

Several factors were important in considering guideline quality. For example, although many guidelines described benefits, adverse effects, and the strength and limitations of evidence or linked the evidence to the recommendation, they often inadequately described how they had considered or weighted these

factors in developing the final recommendations. The guidelines frequently relied on selective reporting of studies or outcomes and focused on relative versus absolute effects and asymptomatic surrogate measures rather than patient-centered health outcomes.

All of the reviewed guidelines recommend individualizing HbA_{1c} targets on the basis of patient characteristics, such as comorbid conditions and risk for hypoglycemia (**Appendix**, available at Annals.org). The ADA and SIGN guidelines recommend a target of 7% for the general population, whereas AACE/ACE recommends 6.5% (if it can be achieved safely). The NICE guideline specifies 6.5% or 7%, depending on the patient's treatment regimen. Both ICSI and VA/DoD recommend target ranges. The ICSI guideline recommends less than 7% to less than 8% based on patient factors, whereas the VA/DoD recommends the following target ranges based on life expectancy and comorbid conditions: 6% to 7% for patients with a life expectancy greater than 10 to 15 years and no or mild microvascular complications; 7% to 8.5% for those with established microvascular or macrovascular disease, comorbid conditions, or a life expectancy of 5 to 10 years; and 8% to 9% for those with a life expectancy less than 5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management attributable to mental status, disability, or other factors (12). All guidelines recognize that HbA_{1c} targets can be higher in patients with comorbid conditions and limited life expectancy.

We looked into the evidence presented in these guidelines, specifically 5 large, long-term randomized trials with a "treat-to-target" strategy and corresponding reports on extended follow-up (16–23). We summarize below the individual studies and resulting benefits and harms. Note that recent studies evaluating the effectiveness and safety of several newer diabetes drugs (for example, recently approved sodium–glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists) were not considered in guideline sections pertaining to HbA_{1c} targets because these studies were not designed to evaluate treat-to-target strategies. Therefore, their findings are not described here.

Benefits and Harms of Lower HbA_{1c} Targets: Evidence From Clinical Trials

Five large, long-term randomized controlled trials investigated intensive (achieved HbA_{1c} levels, 6.3% to 7.4%) versus less intensive (achieved HbA_{1c} levels, 7.3% to 8.4%) treatment target strategies in adults (average baseline age, 53 to 66 years). They found that the main effect of more intensive glycemic control is small absolute reductions in risk for microvascular surrogate events, such as retinopathy detected on ophthalmologic screening or nephropathy defined by development or progression of albuminuria (**Appendix Table 2**, available at Annals.org) (16–23). Studies have not consistently shown that intensive glycemic control to HbA_{1c} levels below 7% reduces clinical microvascular events, such as loss or impairment of vision, end-stage renal disease, or painful neuropathy, or reduces macrovascular events and death. One trial of metformin in overweight adults showed a reduction in all-cause and diabetes-related death through at least 10 years (22).

In all studies, patients randomly assigned to more intensive therapy required more antiglycemic medications at higher doses, which led to more adverse events than in the less intensive groups. In 1 study, very intensive control resulted in an increased risk for death (18).

Appendix Table 2 summarizes data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (18), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (20), UKPDS (United Kingdom Prospective Diabetes Study) (22, 23), and VADT (Veterans Affairs Diabetes Trial) (17) trials.

ACCORD Trial

The ACCORD trial compared the effects of intensive therapy (target HbA_{1c} levels <6.0%) with those of standard therapy (target HbA_{1c} levels, 7.0% to 7.9%; achieved levels, 6.4% vs. 7.5%). Participants had a mean age of 62.2 years and median baseline HbA_{1c} level of 8.1%. The trial was terminated early (mean follow-up, 3.5 years) because of increases in all-cause mortality (hazard ratio [HR], 1.22 [95% CI, 1.01 to 1.46]), cardiovascular-related death (HR, 1.35 [CI, 1.04 to 1.76]), and hypoglycemic events requiring assistance in the group assigned to the lower HbA_{1c} target. Intensive treatment did not reduce risk for major adverse cardiovascular events (HR, 0.90 [CI, 0.78 to 1.04]), fatal or nonfatal stroke, or fatal or nonfatal congestive heart failure. Participants receiving intensive treatment had fewer nonfatal myocardial infarctions (HR, 0.76 [CI, 0.62 to 0.92]). Intensive therapy did not reduce risk for microvascular outcomes (including renal failure, doubling of serum creatinine, visual impairment, retinal photocoagulation, and neuropathy) but led to small absolute reductions in the onset of albuminuria. Additional follow-up through a median of 5 years confirmed the original report's findings (achieved HbA_{1c} levels: intensive group, 7.2%; standard group, 7.6%) (19).

The trial was stopped early because more intensive glycemic control was associated with a 22% increase in all-cause mortality, a 35% increase in cardiovascular-related death, and a 3-fold increase in risk for severe hypoglycemia (18). More intensive treatment also resulted in increased weight gain of more than 10 kg (27.8% vs. 14.1%) and increased fluid retention.

ADVANCE Trial

The ADVANCE trial enrolled participants with a mean baseline age of 66 years and mean baseline HbA_{1c} level of 7.5%. Intensive treatment (HbA_{1c} levels: target ≤6.5%; achieved, 6.5%) compared with standard treatment (achieved HbA_{1c} level, 7.3%) did not reduce major macrovascular events (HR, 0.94 [CI, 0.84 to 1.06]), all-cause mortality (HR, 0.93 [CI, 0.83 to 1.06]), or cardiovascular-related death (HR, 0.88 [CI, 0.74 to 1.04)]) over a median of 5 years (20). Intensive treatment resulted in reduced incidence of combined mac-

rovascular and microvascular events (18.1% vs. 20.0%; HR, 0.90 [CI, 0.82 to 0.98]) and microvascular events (9.4% vs. 10.9%; HR, 0.86 [CI, 0.77 to 0.97]) over a median of 5 years. This was primarily because of a small absolute reduction in the incidence of nephropathy (4.1% vs. 5.2%; HR, 0.79 [CI, 0.66 to 0.93]) mostly due to the development of macroalbuminuria. The lower target did not affect doubling of serum creatinine, neuropathy, retinopathy, or visual deterioration. Effects were consistent across subgroups, including those with a history of microvascular or macrovascular disease.

More severe hypoglycemic events were seen with intensive glycemic control (2.7% vs. 1.5%; HR, 1.86 [CI, 1.42 to 2.40]) (20). Minor hypoglycemia also occurred more frequently, and hospitalization was more common (44.9% vs. 42.8%; HR, 1.07 [CI, 1.01 to 1.13]).

UKPDS Trials

The UKPDS trials involved 2 separate studies evaluating intensive glycemic control versus conventional therapy (diet and subsequent treatments if marked hyperglycemia persisted) in adults (mean age, 54 years) with newly diagnosed type 2 diabetes. One third of participants had retinopathy at baseline. The larger UKPDS 33 trial (23) (n = 3867; mean baseline age, 54 years) compared intensive glycemic control (target fasting plasma glucose level <6 mmol/L [108 mg/dL]; median attained HbA_{1c} level, 7%) using either sulfonylureas or insulin versus less stringent control (target fasting plasma glucose best achievable with diet; median attained HbA_{1c} level, 7.9%) using diet and added hypoglycemic agents if patients developed marked hyperglycemia. At a median follow-up of 10 years, intensive control reduced any diabetes-related end point by a relative 12% (CI, 1% to 21%) (P = 0.029). The absolute difference was 5.1 events per 1000 patient-years. This was largely due to a reduction in the composite outcome of microvascular end points, which comprised retinal photocoagulation for asymptomatic retinal findings detected on screening (relative risk reduction, 25% [CI, 7% to 40%]; P = 0.0099). The study found no differences in diabetes-related death (relative reduction, 10% [CI, −11% to 27%]; P = 0.34), all-cause mortality (relative reduction, 6% [CI, −10% to 20%]; P = 0.44), myocardial infarction, stroke, or amputation (23).

The UKPDS 34 trial (22) assessed intensive therapy with metformin (median attained HbA_{1c} level, 7.4%) versus conventional therapy (median attained HbA_{1c} level, 8.0%), primarily in overweight adults (n = 753). Supplementary and secondary analyses included participants from UKDPS 33 who subsequently received metformin for fasting plasma glucose levels that were persistently high. Compared with the conventional treatment group (receiving dietary advice or additional nonintensive pharmacologic therapy if they had marked hyperglycemia), patients initially allocated to metformin (n = 342) had relative risk reductions of 32% (CI, 13% to 47%) (P = 0.0023) for any diabetes-related end point, 42% (CI, 9% to 63%) (P = 0.017) for diabetes-related death, and 36% (CI, 9% to 55%) (P = 0.011) for all-cause mortality. This equates to absolute reductions in diabetes-related and all-cause mortality of approximately 5 and 7 deaths per 1000 patient-years, respectively. These reductions were greater than those attained with intensive therapy with sulfonylureas or insulin. However, early addition of metformin to sulfonylureas resulted in an increased risk for diabetes-related death (P = 0.039) compared with continued treatment with sulfonylureas alone.

On extended follow-up (median time from randomization, 17 years), 3277 patients originally enrolled in UKPDS 33 or 34 who received intensive glucose control with sulfonylureas or insulin had a 9% relative reduction of borderline statistical significance in any diabetes-related end point (risk ratio, 0.91 [CI, 0.83 to 0.99]; P = 0.04) and an absolute reduction in all-cause mortality (3.5 deaths per 1000 patient-years; P = 0.007) (16). In the metformin-intensive therapy group, risk reductions persisted for any diabetes-related end point (risk reduction, 21%; 8.2 events per 1000 patient-years; P = 0.01), myocardial infarction (risk reduction, 33%; 6.3 events per 1000 patient-years; P = 0.005), and all-cause mortality (risk reduction, 27%; 7.2 deaths per 1000 patient-years; P = 0.002).

Hypoglycemic events were much more common in the intensive than standard treatment groups of the UKPDS trials (approximately 30% vs. 1% annually) (23). Early addition of metformin to sulfonylureas resulted in an increased risk for diabetes-related death (P = 0.039) compared with continued treatment with sulfonylureas alone.

VADT

The VADT compared patients (mean age, 60 years; median baseline HbA_{1c} level, 9.4%) in an intensive therapy group (median achieved HbA_{1c} level, 6.9%) with those in a standard therapy group (median achieved HbA_{1c} level, 8.4%). The trial targeted an absolute between-group difference in HbA_{1c} level of 1.5 percentage points and found no reduction in major cardiovascular events, death, or microvascular events, except for "any increase in albuminuria," over a median follow-up of 5.6 years (21). The intensive therapy group had fewer cardiovascular events over an extended follow-up of about 12 years (HR, 0.83 [CI, 0.70 to 0.99]; P = 0.04). However, the absolute effect was small (8.6 events per 1000 patient-years), and the outcome included hospitalization for new or worsening heart failure and asymptomatic ejection fractions of less than 40%. The investigators found no reduction in all-cause mortality (HR, 1.05 [CI, 0.89 to 1.25]) or cardiovascular-related death (HR, 0.88 (CI, 0.64 to 1.20) (17).

Severe and any hypoglycemia were more common in the intensive therapy group than the standard therapy group. This included a 3-fold higher rate of episodes with impaired consciousness (9 vs. 3 episodes per 100 patient-years). Serious adverse events were also more common in the intensive therapy group (24.1% vs. 17.6%; P = 0.05); dyspnea was the most common (P = 0.006) (21).

GUIDANCE STATEMENTS

Guidance Statement 1: Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

All of the assessed guidelines recommend personalizing HbA_{1c} goals for individual patients (**Appendix**) (7–12). The benefits and harms of more versus less intensive glycemic control may be finely balanced for many persons and vary according to expected duration of treatment, comorbid conditions, risk factors for hypoglycemia, and choice of medication. The choice of glycemic target also depends on consideration of other variables, such as risk for hypoglycemia, weight gain, and other drug-related adverse effects, as well as the patient's age, life expectancy, other chronic conditions, functional and cognitive impairments, fall risk, ability to adhere to treatment, and medication burden and cost.

Guidance Statement 2: Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.

Most of the guidelines referred to 5 trials as the rationale for their HbA_{1c} targets of 7% or 8% (**Appendix Table 2**) (19–23). Collectively, these trials showed that treating to targets of 7% or less compared with targets around 8% did not reduce death or macrovascular events over about 5 to 10 years of treatment but did result in substantial harms, including but not limited to hypoglycemia. Our guidance statement is adapted from and is most consistent with the ICSI guideline, which recommends an HbA_{1c} target range between less than 7% and less than 8% (8). The VA/DoD guideline also specifies ranges rather than specific targets and selects them according to life expectancy, comorbid conditions, and other factors (12). Including ranges for recommended goals also allows for variability in individual HbA_{1c} measurements.

The ICSI guideline highlights that efforts to achieve HbA_{1c} levels below 7% may increase risk for death, weight gain, hypoglycemia, and other adverse effects in many patients (8), and we share these concerns. Of the 3 trials achieving an HbA_{1c} level less than 7%, none showed a reduction in all-cause or cardiovascular-related death (18, 20, 21).

The guidelines recommending lower targets (below 7% or below 6.5%) give the rationale that more intensive glycemic control reduces microvascular events over many years of treatment. Of note, however, the evidence for reduction is inconsistent, and reductions were seen only in surrogate microvascular end points, such as progression of proteinuria or receipt of retinal photocoagulation. Trials did not show substantial reductions in clinical microvascular events. In addition, the ACCORD trial found an increased risk for death with an HbA_{1c} target of less than 6.5% (18).

Most of the guidelines noted that a target in the lower end of the range (7%) applied best to patients with newly diagnosed diabetes and those without substantial diabetes-related complications. The rationale for this is based on results from the UKPDS. This trial showed that treatment to a target of about 7% with a sulfonylurea and insulin (if needed) in adults with newly diagnosed diabetes did not reduce risk for any diabetes-related end point or all-cause mortality after 10 years but was associated with a small absolute reduction in these outcomes after 17 years (16, 23). A substudy (UKPDS 34) also showed a modest reduction in diabetes-related end points and all-cause mortality with metformin in overweight or obese adults (2, 12).

All laboratory measurements, including HbA_{1c} levels, are associated with variability. Therefore, a clinician should consider the variability of HbA_{1c} test results when selecting goals or making therapeutic decisions.

Any benefit of more intensive glycemic control likely requires a long time to manifest. Thus, more stringent targets may be appropriate for patients who have a long life expectancy (>15 years) and are interested in more intensive glycemic control with pharmacologic therapy despite the risk for harms, including but not limited to hypoglycemia, patient burden, and pharmacologic costs.

Although this guidance statement focuses on pharmacologic glycemic control, a lower treatment target is appropriate if achievable with diet and lifestyle modifications. Clinicians should counsel patients and emphasize the importance of lifestyle interventions, including exercise, dietary changes, and weight loss, to achieve good glycemic control. Smoking cessation, adequate blood pressure control, and lipid management are also indicated in patients with type 2 diabetes and, for many patients, may take priority over achieving glycemic control, especially for preventing macrovascular complications.

Guidance Statement 3: Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.

No trials show that targeting HbA_{1c} levels below 6.5% in diabetic patients improves clinical outcomes, and pharmacologic treatment to below this target has substantial harms. The ACCORD trial, which targeted an HbA_{1c} level less than 6.5% and achieved the lowest level of the included studies (6.4%), was discontinued early because of increased overall and cardiovascular-related death and severe hypoglycemic events (18). The ADVANCE study also failed to find a statistically significant clinical benefit and had more adverse effects with an achieved median HbA_{1c} level of 6.4% than with 7.0%. In addition, more intensive treatment to achieve a lower target is more costly and is associated with increased patient burden. Therefore, if a patient achieves an HbA_{1c} level less than 6.5%, the clinician should deintensify treatment by reducing the dosage, removing a medication if the patient is receiving more than 1, or discontinuing pharmacologic treatment.

Although other drugs have been associated with harms, the balance between benefits and harms is uncertain with metformin for lower HbA_{1c} levels. Metformin is not associated with hypoglycemia and is gen-

Figure. Summary of the American College of Physicians guidance statement on HbA_{1c} targets for glycemic control with pharmacologic therapy in nonpregnant adults with type 2 diabetes mellitus.

ACP[SM]
American College of Physicians
Leading Internal Medicine, Improving Lives

Summary of the American College of Physicians Guidance Statement on HbA_{1c} Targets for Glycemic Control With Pharmacologic Therapy in Nonpregnant Adults With Type 2 Diabetes Mellitus

Disease/Condition	**Type 2 diabetes**
Target Audience	**All clinicians**
Target Patient Population	**Outpatient nonpregnant adults with type 2 diabetes**
Outcomes Evaluated	**Microvascular and macrovascular outcomes, mortality**
Benefits	**Reduced microvascular and macrovascular outcomes, reduced mortality**
Harms	**Harms of achieving lower HbA_{1c} targets with pharmacologic interventions include increased hypoglycemia (including severe), hospitalizations, weight gain, water retention, and death.** **Adverse effects associated with pharmacologic treatments for diabetes include but are not limited to gastrointestinal side effects, hypoglycemia, weight gain, congestive heart failure, joint pain, fractures, and genital mycotic infections. These adverse effects increase with higher doses and greater numbers of medications likely required to achieve lower HbA_{1c} levels.**
Guidance Statements	***Guidance Statement 1: Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*** ***Guidance Statement 2: Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*** ***Guidance Statement 3: Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*** ***Guidance Statement 4: Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.***
High-Value Care	**Deescalation of therapy, by reducing dosage or number of drugs, is warranted in many persons with HbA_{1c} levels persistently <6.5% after treatment with drugs. Persons with advanced age and lower life expectancy should be treated to reduce symptoms rather than strictly focusing on specific HbA_{1c} target levels.**
Clinical Considerations	**Encourage a healthy lifestyle (e.g., tobacco cessation, diet and exercise, and attaining ideal body weight), including for risk reduction in patients with known or high risk for cardiovascular disease.** **Consider individual patient-level variables, such as polypharmacy issues, limited life expectancy, extensive multiple comorbid conditions, and cognitive impairment.** **Consider patient preference when deciding on treatment strategies and goals.** **Test results for HbA_{1c} levels can vary because of such conditions as anemia and chronic kidney disease; therefore, clinicians should aim for a target range rather than a specific target.**

To arrive at these guidance statements, the authors reviewed guidelines from the National Institute for Health and Care Excellence, the Institute for Clinical Systems Improvement, the American Association of Clinical Endocrinologists and American College of Endocrinology, the American Diabetes Association, the Scottish Intercollegiate Guidelines Network, and the U.S. Department of Veterans Affairs and Department of Defense. HbA_{1c} = hemoglobin A_{1c}.

erally well-tolerated and low cost, but it is associated with other known adverse effects and results in use of additional medication with little to no benefit at HbA_{1c} levels below 7%. The ACP guideline on oral pharmacologic treatment of diabetes (24) provides information on metformin and other medications.

Guidance Statement 4: Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia,

cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.

All of the evaluated guidelines suggest relaxing HbA_{1c} targets for patients with multiple comorbid conditions, limited life expectancy, or increased risk for hypoglycemia (7–11). Setting stringent targets in these populations is not an optimal approach, and clinicians should instead focus on treating to reduce symptoms from both disease and treatment. The ACP guidance statement in persons with a life expectancy less than 10 years is based on the small death or cardiovascular benefit of lower HbA_{1c} targets through at least 10 years, which should be balanced with treatment harms, including but not limited to hypoglycemia and patient views of treatment burden. For example, a modeling study has examined how treatment burden affects the benefits of intensive versus moderate glycemic control in patients with type 2 diabetes (25). Authors used microvascular benefits shown in UKDPS 33, as well as reductions in congenital heart disease events from observational studies and the long-term follow-up of UKPDS, to assess lifetime benefits of glycemic targets. Even with low estimates of treatment-related adverse effects and patient-perceived treatment burden, achieving more intensive target HbA_{1c} levels of 7.5% or below rather than 8.5% (especially if using insulin) resulted in net harm in most patients aged 55 years or older.

The **Figure** summarizes the guidance statements and clinical considerations.

Multiple Chronic Conditions: Application to Older Populations

Consideration of how this evidence base applies in older populations is important because of the high proportion of older patients with multiple chronic comorbid conditions, the frequency of polypharmacy and potential for drug interactions, and the consequent likelihood that the balance of benefits and harms is different in older patients. For patients with multiple comorbid conditions, including renal failure, liver failure, end-stage disease complications, cognitive impairment, advanced microvascular or macrovascular complications, or any other conditions that limit life expectancy, the harms of more intensive HbA_{1c} targets outweigh the benefits. Many guidelines also discuss the role of less intensive targets for older adults. In these patients, the goal should be to minimize symptoms rather than achieve a specific HbA_{1c} target.

Insufficient Areas of Evidence

Evidence from trials included here is insufficient to evaluate the effect of HbA_{1c} targets between 6.5% and 7% on clinical outcomes, and further research would be needed to close this gap.

High-Value Care

ACP believes that clinicians should reevaluate HbA_{1c} levels and revise treatment strategies on the basis of changes in the balance of benefits and harms due to changed costs of care and patient preferences, general health, and life expectancy. In persons who reach HbA_{1c} levels less than 6.5% with drug treatment, deescalation of therapy (by reducing dosage or number of drugs) is warranted to reduce harms, patient burden, and costs of treatment. Generic medications are preferred when available. ACP recently provided recommendations on pharmacologic treatment of type 2 diabetes (24).

Policy Implication for Performance Measures

ACP suggests that any physician performance measures developed to evaluate quality of care should not have a target HbA_{1c} level below 8% for any patient population and should not have any HbA_{1c} targets for older adults (for example, aged ≥80 years) or younger persons with limited life expectancy due to serious comorbid conditions.

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Note: Guidance statements are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP guidance statements are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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Appendix: Summary and Evaluation of Reviewed Guidelines

AACE/ACE

Recommendations

> Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD [cardiovascular disease] risk factors, comorbid conditions, and risk for hypoglycemia, as well as the patient's psychological status (Grade A; BEL [best evidence level] 1). In general, the goal of therapy should be an A1C level ≤6.5% for most nonpregnant adults, if it can be achieved safely . . . (Grade D; BEL 4). . . .
> In adults with recent onset of T2D [type 2 diabetes] and no clinically significant CVD, glycemic control aimed at normal (or near-normal) glycemia should be considered, with the aim of preventing the development of micro- and macrovascular complications over a lifetime, if it can be achieved without substantial hypoglycemia or other unacceptable adverse consequences (Grade A; BEL 1). . . . A less stringent glucose goal should be considered (A1C 7 to 8%) in patients with history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing DM [diabetes mellitus] in which the A1C goal has been difficult to attain despite intensive efforts, so long as the patient remains free of polydipsia, polyuria, polyphagia, and other hyperglycemia-associated symptoms (Grade A; BEL 1). (9)

Comments

According to the AACE/ACE grading scheme, "Grade A; BEL 1" indicates highest-quality evidence with little or no effect from subjective factors on recommendation (evidence mapped to recommendation) and "Grade D; BEL 4" indicates lowest-quality evidence with little or no effect from subjective factors on recommendation (9).

This guideline is a consensus, expert-based guideline, with no systematic review of evidence. In general, the methods behind the clinical recommendations were not clearly presented. This guideline recommends a very low target HbA_{1c} level in most adults (≤6.5%) if it can be achieved safely, although a higher target (7% to 8%) is recommended in patients with multiple chronic conditions or shorter lifespan.

ADA

Recommendations

> A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). ([Grade] A)
> Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. ([Grade] C)
> Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. ([Grade] B). (10)

Comments

According to the ADA grading scheme, Grade A is "[c]lear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered." Grade B is "[s]upportive evidence from well-conducted cohort studies" (10).

This guideline does not clearly present methods or details about the systematic reviews that were used to develop the recommendations. It states that HbA_{1c} targets should be less than 7% in most adults, even more stringent (<6.5%) in select cases treated with lifestyle or

metformin alone, and less stringent (<8%) in patients with multiple chronic conditions.

ICSI

Recommendation

> A clinician should personalize goals with patients diagnosed with T2DM [type 2 diabetes mellitus] to achieve glycemic control with a hemoglobin A1c < 7% to < 8% depending on individual patient factors [strong recommendation, high-quality evidence]. (8)

Comments

The ICSI clearly presents the evidence and methodology behind their clinical recommendations. It specifies that an HbA_{1c} target of less than 8% may be more appropriate than 7% in persons with cardiovascular disease or high cardiovascular risk, history of severe hypoglycemia requiring assistance, polypharmacy issues, limited life expectancy (<10 years), cognitive impairment, or extensive comorbid conditions (renal or liver failure or end-stage disease complications). It highlights that efforts to achieve HbA_{1c} levels below 7% may increase risk for death, weight gain, hypoglycemia, and other adverse effects in many patients.

NICE

Recommendations

> Involve adults with type 2 diabetes in decisions about their individual HbA1c target. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life. . . .
>
> For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%). . . .
>
> In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:
>
> • reinforce advice about diet, lifestyle and adherence to drug treatment and
>
> • support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and
>
> • intensify drug treatment. . . .
>
> Consider relaxing the target HbA1c level . . . on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:
>
> • who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy
>
> • for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job
>
> • for whom intensive management would not be appropriate, for example, people with significant comorbidities. (7)

Comments

The NICE guideline is based on a clear description of the benefits and harms of tight glycemic control. It encourages patients to be involved in decisions about their HbA_{1c} target. Target levels range from 6.5% when only diet and exercise are used to manage diabetes, 7% when patients are treated with monotherapy associated with hypoglycemia, and 7.5% when they are treated with combination therapy. The guideline stresses an individualized approach in patients with multiple chronic conditions or limited life expectancy, although it does not define limited life expectancy.

SIGN

Recommendations

> An HbA1c target of 7.0% (53 mmol/mol) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycemia and weight gain (Grade A). (11)

Comments

According to the SIGN grading scheme, grade A corresponds to at least 1 meta-analysis, systematic review, or randomized controlled trial rated as high quality and directly applicable to the target population or a body of evidence consisting principally of studies rated well with low risk of bias, directly applicable to the target population, and showing overall consistency of results (11).

The SIGN guideline is based on a clear description of the benefits and harms of tight glycemic control. It recommends an HbA_{1c} target less than 7%. It also recommends individualized targets with no clarity on specific target levels when individualized.

VA/DoD

Recommendations

> We recommend setting an HbA1c target range based on absolute risk reduction of significant microvascular complications, life expectancy, patient preferences and social determinants of health. [Strong recommendation]

We recommend developing an individualized glycemic management plan, based on the provider's appraisal of the risk-benefit ratio and patient preferences. [Strong recommendation]
We recommend assessing patient characteristics such as race, ethnicity, chronic kidney disease, and non-glycemic factors (e.g., laboratory methodology and assay variability) when interpreting HbA1c, fructosamine and other glycemic biomarker results. [Strong recommendation]
We recommend an individualized target range for HbA1c taking into account individual preferences, presence or absence of microvascular complications, and presence or severity of comorbid conditions. [Strong recommendation]
We suggest a target HbA1c range of 6.0-7.0% for patients with a life expectancy greater than 10-15 years and absent or mild microvascular complications, if it can be safely achieved. [Weak recommendation]
We recommend that in patients with type 2 diabetes, a range of HbA1c 7.0-8.5% is appropriate for most individuals with established microvascular or macrovascular disease, comorbid conditions, or 5-10 years life expectancy, if it can be safely achieved. [Strong recommendation]
We suggest a target HbA1c range of 8.0-9.0% for patients with type 2 diabetes with life expectancy <5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management attributable to e.g., mental status, disability or other factors such as food insecurity and insufficient social support. [Weak recommendation]
We suggest that providers be aware that HbA1c variability is a risk factor for microvascular and macrovascular outcomes. [Weak recommendation] (12)

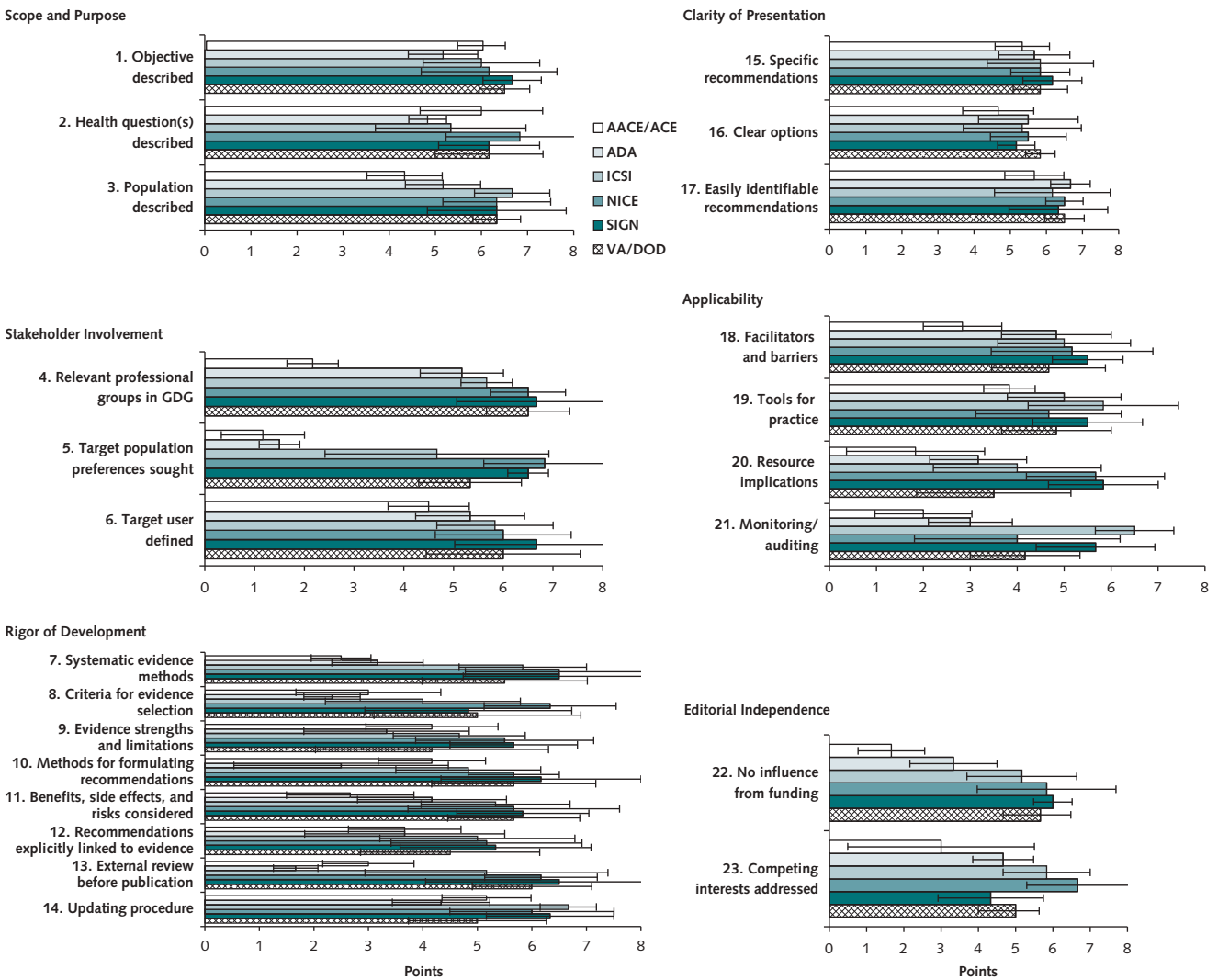
Comments

The VA/DoD guideline is based on a description of the benefits and harms of glycemic control. It emphasizes the importance of shared decision making in setting HbA_{1c} goals and recommends target ranges based on comorbid conditions, life expectancy, and other factors rather than setting a fixed target HbA_{1c} level. It emphasizes that the lower targets of 6.0% to 7.0% and 7.0% to 8.5% should be attained if they can be reached safely.

Web-Only References

26. **Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al; ACCORD trial group.** Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376:419-30. [PMID: 20594588] doi:10.1016/S0140-6736(10)60576-4

Appendix Figure. Mean AGREE II scores for items in each domain across the 6 reviewers.



Each question was rated on a Likert scale with a minimum of 1 point and a maximum of 7 points. The scores were averaged for each of the 6 reviewers. Error bars represent calculated standard deviation. AACE/ACE = American Association of Clinical Endocrinologists and American College of Endocrinology; ADA = American Diabetes Association; AGREE II = Appraisal of Guidelines for Research and Evaluation II; GDG = guideline development group; ICSI = Institute for Clinical Systems Improvement; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guidelines Network; VA/DoD = U.S. Department of Veterans Affairs and Department of Defense.

Appendix Table 1. Scaled AGREE II Domain Scores for Each Guideline and Overall Assessment

Variable	AACE/ ACE	ADA	ICSI	NICE	SIGN	VA/DoD
Scaled domain score, %*						
Scope and purpose	74	68	83	91	90	89
Stakeholder involvement	27	50	73	91	94	82
Rigor of development	42	36	70	81	82	70
Clarity of presentation	70	82	80	82	81	84
Applicability	27	50	72	65	77	55
Editorial independence	21	49	74	86	68	72
Overall guideline assessment†						
Average overall quality rating‡	2.8	3.7	5.3	5.7	5.8	5.7
I would recommend this guideline for use	6 no	1 yes 4 yes with modifications 1 no	3 yes 3 yes with modifications§	3 yes 3 yes with modifications§	3 yes 3 yes with modifications§	3 yes 3 yes with modifications§

AACE/ACE = American Association of Clinical Endocrinologists and American College of Endocrinology; ADA = American Diabetes Association; AGREE II = Appraisal of Guidelines for Research and Evaluation II; ICSI = Institute for Clinical Systems Improvement; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guidelines Network; VA/DoD = U.S. Department of Veterans Affairs and Department of Defense.

* Calculated as follows: (obtained score − minimum possible score) ÷ (maximum possible score − minimum possible score).

† Final overall assessment questions on AGREE II.

‡ Out of 7 possible points; average score from all raters.

§ Although this guideline scored high on the AGREE II domains and was methodologically sound, the reviewers did not fully agree with its final recommendations and therefore recommend with modifications.

Appendix Table 2. Study, Patient, and Outcome Characteristics of Major Type 2 Diabetes Trials Included in the Assessed Guidelines

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
ACCORD, 2008 (18) Mean: 3.5 y *n* = 10 251	62.2	10 y (35% with prior CV event)	Median: 8.1 vs. 8.1	Median: 6.4 vs. 7.5	MACE* (first occurrence of nonfatal MI, nonfatal stroke, or death from CVD): HR, 0.90 (95% CI, 0.78 to 1.04); 6.9% vs. 7.2% No difference in microvascular outcomes (including renal failure, creatinine doubling, visual impairment, retinal photocoagulation, and neuropathy)	All-cause mortality: HR, 1.22 (95% CI, 1.01 to 1.46) Trial stopped early due to increased all-cause mortality, which did not vary by baseline sex, age, HbA_{1c} level, race, or previous CV event CV mortality: HR, 1.35 (95% CI, 1.04 to 1.76); 2.6% vs. 1.8%	Nonfatal MI: HR, 0.76 (95% CI, 0.62 to 0.92); 3.6% vs. 4.6% Nonfatal stroke: HR, 1.06 (95% CI, 0.75 to 1.50) Fatal/nonfatal CHF: HR, 1.18 (95% CI, 0.93 to 1.49)	Hypoglycemia (requiring assistance): 10.5% vs. 3.5%; $P < 0.001$ Any nonhypoglycemic serious AEs: 2.2% vs. 1.6%; $P = 0.03$ Mean weight gain: 3.5 kg vs. 0.4 kg Weight gain >10 kg: 27.8% vs. 14.1%; $P < 0.001$ Fluid retention: 70.1% vs. 66.8%; $P < 0.001$ Greater use of oral hypoglycemic drugs and insulin
ACCORD, 2010 (26) ACCORD, 2011 (19) Mean extended follow-up: 4.9 y				Median: 7.2 vs. 7.6	MACE*: HR, 0.91 (95% CI, 0.81 to 1.03) "First composite microvascular complications" (development of renal failure, retinal photocoagulation, or vitrectomy to treat retinopathy): HR, 0.95 (95% CI, 0.85 to 1.07) "2nd composite microvascular complications" (first composite + Michigan neuropathy screening instrument score >2.0): HR, 0.95 (95% CI, 0.89 to 1.01)	All-cause mortality: HR, 1.19 (95% CI, 1.03 to 1.38); 1.53 vs.1.27 CV mortality: HR, 1.29 (95% CI, 1.04 to 1.60); 0.74% vs. 0.57%	Nonfatal MI: HR, 0.82 (95% CI, 0.70 to 0.96); 1.18 vs. 1.42 Fatal/nonfatal stroke: HR, 0.86 (95% CI, 0.65 to 1.13) Fatal/nonfatal CHF: HR, 1.09 (95% CI, 0.91 to 1.32)	

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
ADVANCE, 2008 (20) Median: 5 y *n* = 11 140	Mean: 66.0	7.9 y (32% with prior CVD)	Mean: 7.5 vs. 7.5 Median: 7.2 vs. 7.2	Mean: 6.5 vs. 7.3 Median: 6.4 vs. 7.0	Combined major macrovascular and microvascular events*: HR, 0.90 (95% CI, 0.82 to 0.98); ARR, 1.9%; 18.1% vs. 20.0% Results were similar regardless of baseline micro/macrovascular disease status Major microvascular events: HR, 0.86 (95% CI, 0.77 to 0.97); 9.4% vs. 10.9% (primarily due to reduction in nephropathy incidence [HR, 0.79 {95% CI, 0.66 to 0.93}] mostly development of macroalbuminuria 2.9% vs. 4.1% without effect on doubling of serum creatinine level or renal replacement therapy) New or worsening neuropathy or retinopathy and visual deterioration were not significantly reduced	All-cause mortality: HR, 0.93 (95% CI, 0.83 to 1.06) CV mortality: HR, 0.88 (95% CI, 0.74 to 1.04)	Macrovascular events: HR, 0.94 (95% CI, 0.84 to 1.06) Nonfatal MI: RRR, 2% (95% CI, −23% to 22%) All CV events: RRR, 2% (95% CI, −10% to 13%) Heart failure: RRR, 5% (95% CI, −14% to 21%) Nonfatal stroke: RRR, −2% (95% CI, −24% to 15%)	Severe hypoglycemia: HR, 1.86 (95% CI, 1.42 to 2.40); 2.7% vs. 1.5%; 0.7 vs. 0.4 per 100 patient-years Minor hypoglycemia: 120 vs. 90 per 100 patient-years Hospitalization: 44.9% vs. 42.8%; HR, 1.07 (95% CI, 1.01 to 1.13) Greater use of oral hypoglycemic drugs and insulin

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
UKPDS 33, 1998 (23) Sulfonylurea ± insulin ± metformin Median: 11.1 y *n* = 3867	54	Newly diagnosed (36% with retinopathy)		Median: 7.0 vs. 7.9	Any diabetes-related end point* (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in 1 eye or cataract): RR, 0.88 (95% CI, 0.79 to 0.99); 40.9 vs. 46.0 per 1000 patient-years Results did not vary by use of sulfonylurea or insulin for intensive control Microvascular end point: RR, 0.75 (95% CI, 0.60 to 0.93); 8.6 vs. 11.4 per 1000 patient-years Retinal photocoagulation: RR, 0.71 (99% CI, 0.53 to 0.96); 7.9 vs. 11.0 per 1000 patient-years	All-cause mortality: HR, 0.94 (95% CI, 0.80 to 1.10) Diabetes-related mortality: HR, 0.90 (95% CI, 0.78 to 1.11) Fatal MI: RR, 0.94 (95% CI, 0.68 to 1.30) Fatal stroke: RR, 1.17 (95% CI, 0.54 to 2.54)	No single macrovascular end point was statistically significant, including nonfatal MI, heart failure, angina, nonfatal stroke, amputation, renal failure; risk differences were ≤2 per 1000 patient-years	Increased hypoglycemia, including major hypoglycemia Major hypoglycemic episodes per year: chlorpropamide, 1.0%; glibenclamide, 1.4%; insulin, 1.8%; and diet, 0.7%; all $P < 0.0001$ Any hypoglycemic episodes: chlorpropamide, 16%; glibenclamide, 21%; insulin, 28%; diet, 10% Hypoglycemic episodes in patients on diet therapy were reactive and occurred either after meals or after termination of glucose infusions given while in hospital Weight gain: 3.1 kg (99% CI, –0.9 to 7.0 kg); $P < 0.0001$

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
UKPDS 34, 1998 (22) Metformin Median: 10.7 y *n* = 753 Sulfonylurea or insulin added if hyperglycemic symptoms developed	53	New diagnosis (35% with retinopathy)	Median: 7.2	Median: 7.4 vs. 8.0	Any diabetes-related end point*: RR, 0.68 (95% CI, 0.53 to 0.87) (mostly clinical and macrovascular but includes photocoagulation); 43.3 vs. 29.8 per 1000 patient-years Microvascular: RR, 0.71 (95% CI, 0.42 to 1.19) Sulfonylurea + metformin, any DM end point: RR, 1.04 (95% CI, 0.77 to 1.42)	Any diabetes-related death: RR, 0.58 (95% CI, 0.37 to 0.91); 7.5 vs. 12.7 per 1000 patient-years All-cause mortality: RR, 0.64 (95% CI, 0.45 to 0.91); 13.5 vs. 20.6 per 1000 patient-years Fatal stroke: RR, 0.75 (95% CI, 0.19 to 2.93) Fatal MI: RR, 0.50 (95% CI, 0.23 to 1.09) Early addition of metformin to sulfonylureas resulted in increased all-cause mortality: RR, 1.60 (95% CI, 1.02 to 2.52) and diabetes-related death: RR, 1.96 (95% CI, 1.02 to 3.75), compared with continued sulfonylurea alone	MI: RR, 1.09 (95% CI, 0.67 to 1.18) Stroke: RR, 1.21 (95% CI, 0.58 to 2.65) No significant difference in heart failure, angina, nonfatal stroke, amputation, or renal failure	The addition of metformin to sulfonylurea was associated with a 96% increased risk for diabetes-related death ($P = 0.039$); addition of metformin to sulfonylurea therapy also increased the risk for death from any cause (60% increase; $P = 0.041$)

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
UKPDS 33, 2008 (16) Follow-up for sulfonylurea Median: 16.8 y *n* = 3867				Median: 7.9 vs. 8.5	Any diabetes-related end point*: RR, 0.91 (95% CI, 0.83 to 0.99); 48.1 vs. 52.2 per 1000 patient-years Microvascular disease: RR, 0.76 (95% CI, 0.64 to 0.89); 11.0 vs. 14.2 per 1000 patient-years	All-cause mortality: RR, 0.87 (95% CI, 0.79 to 0.96); 26.8 vs. 30.3 per 1000 patient-years Diabetes-related mortality: HR, 0.83 (95% CI, 0.73 to 0.96); 14.5 vs. 17.0 per 1000 patient-years	MI: RR, 0.85 (95% CI, 0.74 to 0.97); 16.8 vs. 19.6 per 1000 patient-years Stroke: RR, 0.91 (95% CI, 0.73 to 1.13) Peripheral vascular disease: RR, 0.82 (95% CI, 0.56 to 1.19)	
UKPDS 34, 2008 (16) Follow-up for metformin Median: 17.7 y n = 753				Median: 8.4 vs. 8.9	Any diabetes-related end point*: RR, 0.79 (95% CI, 0.66 to 0.95); 45.7 vs. 53.9 per 1000 patient-years Microvascular disease: RR, 0.84 (95% CI, 0.60 to 1.17); 12.4 vs. 13.4 per 1000 patient-years	All-cause mortality: RR, 0.73 (95% CI, 0.59 to 0.89); 25.9 vs. 33.1 per 1000 patient-years Diabetes-related mortality: HR, 0.70 (95% CI, 0.53 to 0.92); 14.0 vs. 18.7 per 1000 patient-years	MI: RR, 0.67 (95% CI, 0.51 to 0.89); 14.8 vs. 21.1 per 1000 patient-years Stroke: RR, 0.80 (95% CI, 0.50 to 1.27) Peripheral vascular disease: RR, 0.63 (95% CI, 0.32 to 1.27)	

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
VADT, 2009 (21) Median: 5.6 y *n* = 1791	Mean: 60.4	11.5 y (prior CVD: 40.7%)	Median: 9.4	Median: 6.9 vs. 8.4	Microvascular complications: No difference between intensive and standard control, including ophthalmologic disorder (cataract surgery, photocoagulation, vitrectomy, retinopathy [progression to proliferative disease, progression to clinically significant macular edema, increase of 2 steps in severity of disease, new onset]); neuropathy (including any, mononeuropathy, peripheral, autonomic); nephropathy (doubling of serum creatinine; creatinine level >3 mg/dL; GFR <15 mL/min) Any increase in albuminuria, 9.1% vs. 13.8%; *P* < 0.01	All-cause mortality: HR, 1.07 (95% CI, 0.81 to 1.42) CV mortality: HR, 1.32 (95% CI, 0.81 to 2.14)	MACE* (MI; stroke; death from CV causes; new or worsening CHF; surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease; inoperable coronary artery disease; amputation for ischemic gangrene): HR, 0.88 (95% CI, 0.74 to 1.05) (or any component of MACE)	Hypoglycemic episode with impaired consciousness: 9 vs. 3 per 100 patient-years; *P* < 0.001 Hypoglycemia with complete loss of consciousness: 3 vs. 1 per 100 patient-years; *P* < 0.001 Hypoglycemia as serious AE: 8.5% vs. 3.1%; *P* < 0.0001 With documented glucose <50 mg/dL: 203 vs. 52 per 100 patient-years; *P* < 0.001 Any serious AE: 24.1% vs. 17.6%; *P* = 0.05 Dyspnea: 11.0% vs. 7.2%; *P* = 0.006 End of study weight: 232 lb vs. 223 lb; *P* = 0.01 BMI: 33.8 vs. 32.3 kg/m^2; *P* = 0.01

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Appendix Table 2–Continued

Study, Year (Reference) Mean or Median Follow-up Patients Enrolled	Age at Baseline, *y*	Diabetes Duration	Intensive vs. Control					
			HbA_{1c} Level, %		Microvascular and Combined Microvascular/ Macrovascular Events	Mortality	Macrovascular Events	AEs
			Baseline	Achieved				
VADT, 2015 (17) follow-up Median: 11.8 y				~8.2	MACE* (time to first major CV event: heart attack, stroke, new or worsening CHF [including hospitalization with EF <40%], amputation for ischemic gangrene, or CV-related death): HR, 0.83 (95% CI, 0.70 to 0.99); 44.1 vs. 52.7 per 1000 person-years Results did not differ between patients with lower overall vs. higher overall CV risk at baseline or with respect to a prior CV event or baseline HbA_{1c}	All-cause mortality: HR, 1.05 (95% CI, 0.89 to 1.25) CV mortality: HR, 0.88 (95% CI, 0.64 to 1.20)		

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CHF = congestive heart failure; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; EF = ejection fraction; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; RR = relative risk; RRR = relative risk reduction; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.
* Primary study outcome.

SECTION -3

● Influence of Fruit on Glycemic Control

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SYSTEMATIC REVIEW WITH META-ANALYSIS

100 % Fruit juice and measures of glucose control and insulin sensitivity: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Studies on the effects of consuming 100 % fruit juice on measures of glycaemic control are conflicting. The purpose of the present study was to systematically review and quantitatively summarise results from randomised controlled trials (RCT) examining effects of 100 % fruit juice on glucose–insulin homeostasis. Eligible studies were identified from a systematic review of PubMed and EMBASE and hand searches of reference lists from reviews and relevant papers. Using data from eighteen RCT, meta-analyses evaluated the mean difference in fasting blood glucose (sixteen studies), fasting blood insulin (eleven studies), the homeostatic model assessment of insulin resistance (HOMA-IR; seven studies) and glycosylated Hb (HbA1c; three studies) between the 100 % fruit juice intervention and control groups using a random-effects model. Compared with the control group, 100 % fruit juice had no significant effect on fasting blood glucose (−0·13 (95 % CI −0·28, 0·01) mmol/l; $P = 0·07$), fasting blood insulin (−0·24 (95 % CI −3·54, 3·05) pmol/l; $P = 0·89$), HOMA-IR (−0·22 (95 % CI −0·50, 0·06); $P = 0·13$) or HbA1c (−0·001 (95 % CI −0·38, 0·38) %; $P = 0·28$). Results from stratified analyses and univariate meta-regressions also largely showed no significant associations between 100 % fruit juice and the measures of glucose control. Overall, findings from this meta-analysis of RCT suggest a neutral effect of 100 % fruit juice on glycaemic control. These findings are consistent with findings from some observational studies suggesting that consumption of 100 % fruit juice is not associated with increased risk of diabetes.

Key words: 100 % Fruit juice: Fasting blood glucose: Fasting blood insulin: Insulin sensitivity: Homeostatic model assessment of insulin resistance

Worldwide, the number of people with diabetes is rising. In 2014, the estimated prevalence among adults was 8·5 %, which is approximately double the prevalence of 4·7 % in 1980[1]. Due to its prevalence and associated complications, diabetes is a well-recognised public health concern[2]. Overweight and obesity are the strongest risk factors for type 2 diabetes (T2D), though lifestyle and dietary modification also are recognised strategies that may delay or prevent development of the disease.

Controversy and uncertainty have been expressed within the scientific community as to what effect, if any, 100 % fruit juice may have on health including risk for diabetes[3]. Pure (100 %) fruit juices can be nutrient-dense foods providing K, Mg, folate, Ca, vitamins A and C, and soluble fibre as well as an array of bioactive substances including carotenoids and flavonoids[4–6]. Nutritional guidance encourages consumption of fruit as part of a balanced and healthy diet, although guidance often recommends limited consumption of fruit in the form of juice citing concerns over a lack of fibre and the potential for excessive energy intake[7]. Juices also tend to have moderately high-glycaemic index ratings[8], indicating a relatively rapid and high post-prandial glucose response as compared with foods with a lower glycaemic index, and diets lower in these types

Abbreviations: HbA1c, glycosylated Hb; HOMA-IR, homeostatic model assessment of insulin resistance; RCT, randomised controlled trial; T2D, type 2 diabetes.

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of simple carbohydrates may be relevant for the prevention and management of some chronic diseases including T2D[9]. However, results from *in vitro* and animal studies suggest that polyphenols may favourably affect glucose–insulin homeostasis through a variety of mechanisms[10]. The net effect of 100 % fruit juice on glucose metabolism and biomarkers of diabetes therefore reflects a complex interplay of numerous factors.

Results from human studies of associations between 100 % fruit juice consumption and risk of T2D or effects on diabetes biomarkers have been conflicting. A recent meta-analysis of thirteen prospective cohorts reported no association between consumption of fruit juice and incident T2D[11]. When further adjusted for obesity, the meta-analysis showed a 7 % increased risk for incident T2D, though the presence of significant heterogeneity limits the quality of this evidence[11].

No meta-analysis of randomised controlled trials (RCT) with a specific focus on 100 % fruit juices has been identified. Wang *et al.*[12] reported finding no significant effect on glycaemic control and blood insulin in a meta-analysis of twelve RCT collectively described as 100 % fruit juice. The analysis included studies using juice products other than 100 % fruit juice[12], namely beverages prepared from freeze-dried whole fruit which provided a substantial source of dietary fibre[13,14], beverages prepared from fruit juice sweetened using no-energy sweeteners[15,16], and a study in which both the test and control beverages were prepared from 100 % fruit juice[17]. The identified meta-analysis therefore was not exclusively based on RCT of 100 % fruit juice compared with a non-juice control. Several years have passed since completion of the meta-analysis and recent clinical trials examining the effects of 100 % fruit juice consumption on glucose–insulin homeostasis provide further insight into the role of juice on biomarkers of diabetes risk.

The purpose of the present study was to systematically review the literature to identify RCT in which effects of 100 % fruit juice on measures of glucose control and insulin sensitivity have been examined and, based on the totality of evidence, to re-evaluate in a meta-analysis the effects of 100 % fruit juice on these biomarkers for diabetes risk.

Methods

Literature search and study selection

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18]. A comprehensive literature search was conducted to identify clinical studies examining the relationship between the consumption of 100 % fruit juice and measures of glucose–insulin homeostasis, with no exclusions based on age, ethnicity or health status of the study population. A pre-specified protocol is not available for this study. The search of PubMed was conducted with terms (juice[TIAB] OR juices[TIAB]) AND ('controlled trial' OR 'clinical trial' OR crossover OR cross-over OR random*) with no limits other than English-language papers. The search of EMBASE was conducted using similar terms. Terms for specific measures of glucose control or insulin sensitivity were not included in the search string to allow for identification of studies in which measures of interest were collected as secondary outcomes or in the course of routine patient monitoring. The initial search was conducted on 23 March 2015, and searches were updated on 14 April 2016. Supplemental literature searches included review of reference lists in relevant studies and pertinent review articles and correspondence with researchers in the field.

The search results were screened independently by two investigators (M. M. M., E. C. B.) for eligible studies and discrepancies were resolved by consensus. Clinical trials were eligible if the following criteria were met: (1) the trial was randomised and conducted in human subjects; (2) the trial was a controlled intervention providing 100 % fruit juice and a control beverage (e.g. sugar/carbohydrate or energy-matched beverage, water, or no beverage); (3) the fruit juice consumed was identified as 100 % fruit juice (including single-strength juice prepared from concentrate or a blend of 100 % fruit juices) or any juice specified by name such as, but not limited to, apple, blueberry, cherry, cranberry, grape, grapefruit, orange, pear, pomegranate or strawberry juice; (4) subjects consumed 100 % fruit juice for a minimum of 2 weeks; (5) outcome data for at least one measure of glucose control or insulin sensitivity were reported; and (6) reported outcomes included change from baseline values or baseline and endpoint values with error terms. Tomato juice was not included as a fruit juice in this analysis as it is typically marketed as a vegetable juice.

Data extraction

All eligible studies were reviewed and pertinent data were extracted, including: name of the first author, publication year, study design, geographic location of the intervention, demographic and health characteristics of the study population (e.g. age, sex, presence of obesity or a chronic disease, BMI), sample size, intervention duration, juice type, a description of the control product, and outcomes measured. Additional data extracted from the studies included sugar content of the 100 % fruit juice and control beverages, volume of juice consumed per d, baseline fasting blood glucose level, information on randomisation, double-blinding, and withdrawals and dropouts to develop quality scores of each study based on the Jadad criteria[19]. Information on funding was reviewed to determine if the research was completed with support from industry funding, including donation of study product. Data extraction was completed independently by one investigator and reviewed for accuracy by another (M. M. M. and E. C. B. or K. A. B.). The extracted information included that provided by study investigators in response to requests for missing data and study details[20–23]. Fasting blood glucose, fasting blood insulin, the homeostatic model assessment of insulin resistance (HOMA-IR), glycosylated Hb (HbA1c) and other reported measures of glucose–insulin homeostasis (oral glucose tolerance test, insulinogenic and Matsuda indices) were captured as change from baseline or as baseline and post-intervention values. Fasting glucose values were converted to

mmol/l assuming 1 mg/dl = 0·05551 mmol/l. Fasting insulin values were converted to pmol/l assuming 1 μU/ml = 6·0 pmol/l[24].

Statistical analysis

A meta-analysis was conducted to quantify the effects of consumption of 100 % fruit juice on each measure of glucose control or insulin sensitivity reported in at least three studies. The meta-analysis evaluated the mean difference from baseline and end of treatment values between the 100 % juice treatment and control group of fasting blood glucose, fasting blood insulin, HOMA-IR and HbA1c. The I^2 statistic was used to assess statistical heterogeneity between studies.

For studies not reporting the change from baseline to the end of intervention in both the treatment and control groups, the mean difference was calculated as $(\text{Treatment}_{\text{end}} - \text{Treatment}_{\text{baseline}}) - (\text{Control}_{\text{end}} - \text{Control}_{\text{baseline}})$. The method described by Curtin *et al.*[25] was used to estimate the mean difference and associated standard error from the combined parallel and cross-over studies. A pooled estimate of the variance of the mean difference was estimated for each study. For parallel studies, the estimate was derived using the reported estimates of the standard errors or the calculated standard errors as derived from the reported CI estimates. For cross-over studies when estimates of the standard deviation (or standard error) were only available for baseline and post-intervention measurements, the pooled variance was estimated using standard errors for the intervention and control groups and an imputed correlation coefficient of 0·5[26,27] following the approach described by Higgins & Green[27]. The correlation coefficient (0·5) assumed in the derivation was similar to the average coefficient derived from a study in which variances were provided for baseline, treatment end, and change from baseline measures of fasting blood glucose and HOMA-IR; the correlation coefficient for fasting blood insulin derived from this study was 0·7[28]. Hence, a sensitivity analysis assuming a correlation coefficient of 0·7 was conducted for fasting blood insulin.

A random-effects model was used to determine the mean and 95 % CI of differences in changes from baseline between 100 % juice and control groups. The approach described in DerSimonian & Laird[29] was used to conduct the random-effects model. Stratified analyses by study characteristics were planned *a priori* to investigate sources of heterogeneity and univariate meta-regressions were conducted for further investigation. For each of the biomarkers of diabetes, analyses were conducted for type of fruit juice (apple, berry, blend, citrus, grape, pomegranate), type of control beverage (beverage matched for carbohydrate or sugar and/or energy, beverage without carbohydrate or sugar and/or energy, no beverage), volume of intervention beverage (as reported in the original studies for the meta-regression analysis, and categorised as ≤250 ml/d, >250 ml/d in the stratified analysis), duration of

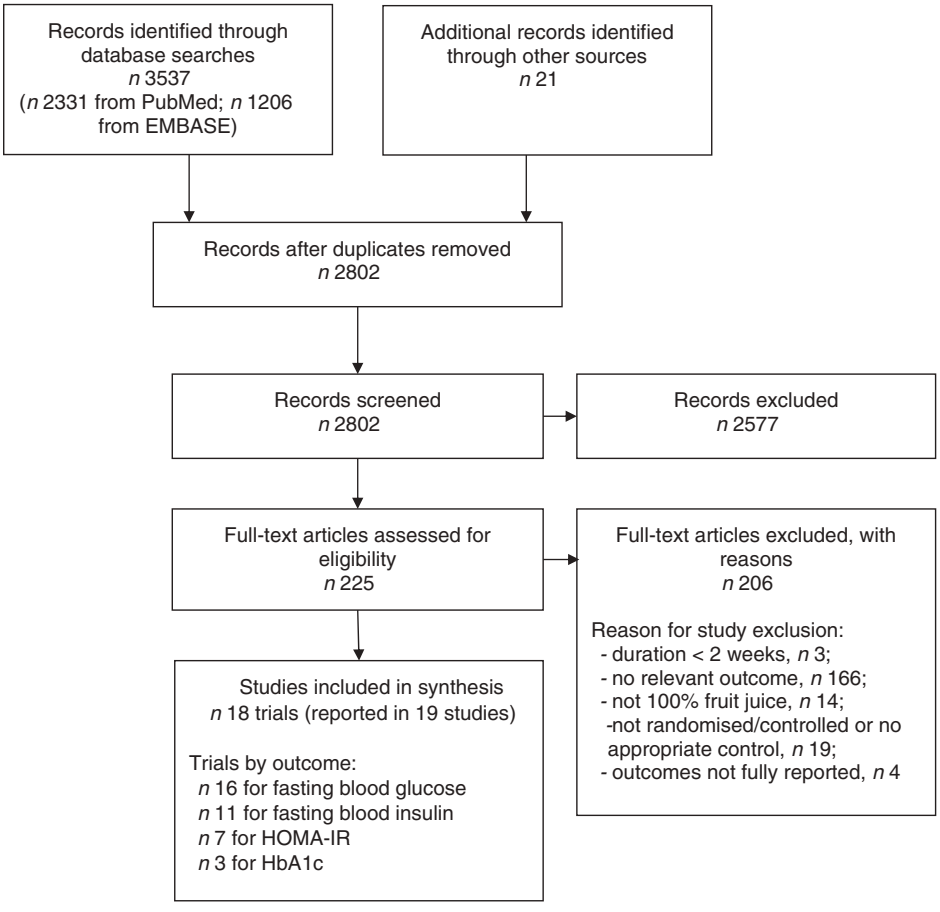

Fig. 1. Flow diagram of study selection process. HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycosylated Hb.

Table 1. Characteristics of eighteen randomised controlled trials of 100 % fruit juice included in analysis

Reference	Location: continent (country)	Study population: health, sex, mean age (years) ± SD	Study design	Mean baseline BMI (kg/m^2) ± SD	Subjects: test/control (*n*)	Mean baseline glucose (mmol/l)	Duration*	Juice test product†: type (ml/d), sugars (g/d)	Control product	Outcome(s), primary or secondary	Industry funding‡
Banini *et al.* (2006)[35]	North America (USA)	Healthy; M/F Test: 50 ± 13 Control: 56 ± 7·5	Parallel	Test: 29·3 ± 4·0 Control: 27·5 ± 5·4	8/15	<5·6	4 weeks	Grape (muscadine) 150, about 23 (estimated)	No beverage	FBG/FBI/ HbA1c, P	Yes
Cerdá *et al.* (2006)[20]	Europe (Spain)	COPD; M Test: 60 ± 10·9 Control: 63·4 ± 8·9	Parallel	Test: 31·4 ± 4·8 Control: 30·6 ± 5·8	15/15	≥5·6	5 weeks	Pomegranate 400, about 53 (estimated)	Sugar-free bev	FBG, S	No
Codoñer-Franch *et al.* (2010)[36]	Europe (Spain)	Obese; M/F Test: 11·8 ± 2·4 Control: 12·1 ± 1·9	Parallel	Test: 29·3 ± 3·5 Control: 28·7 ± 4·2	20/20	<5·6	4 weeks	Mandarin 500, 53	No beverage	FBG/FBI/ HOMA-IR, S	Yes
Dohadwala *et al.* (2010)[37]	North America (USA)	HTN/pre-HTN; M/F Test: 41 ± 13 Control: 44 ± 11	Cross-over	Test: 28 ± 3·8 Control: 28 ± 3·9	64/64	<5·6	8 weeks	Grape (Concord) 595§, 97	Sugar bev	FBG/FBI/ HOMA-IR, S	Yes
González-Ortiz *et al.* (2011)[21]	North America (Mexico)	Obese; F Test: 36·3 ± 8·3 Control: 38·3 ± 10·4	Parallel	Test: 35·2 ± 3·1 Control: 33·8 ± 4·1	10/10	<5·6	1 month	Pomegranate 120, about 16 (estimated)	Sugar-free bev	FBG/FBI/ other, P	No
Guo *et al.* (2014)[38]	Asia (China)	NAFLD; M/F 21·2 ± 1·2	Cross-over	Test: 25·3 ± 2·2 Control: 25·6 ± 2·5	44/43	<5·6	4 weeks	Bayberry 500, 46	Sugar bev	FBG, S	No
Habauzit *et al.* (2015)[39]	Europe (France)	Healthy; F 57·8 ± 3·7	Cross-over	25·7 ± 2·3	48/48	<5·6	6 months	Grapefruit (white) 340, 27	Sugar bev	FBG/FBI/ HOMA-IR, S	Yes
Hollis *et al.* (2009)[33]	North America (USA)	Overweight; M/F Test: 22 ± 4 Control: 26 ± 9	Parallel	Test: 27·0 ± 1·6 Control: 27·0 ± 1·5	25/26	<5·6	12 weeks	Grape (Concord) 480, 82	Sugar bev	FBG, S	Yes
Krikorian *et al.* (2012)[40]	North America (USA)	MCI; M/F 76·9 ± 6·1	Parallel	Not reported	10/11	≥5·6	16 weeks	Grape (Concord) 532§, about 80 (estimated)	Sugar bev	FBG/FBI, S	Yes
Morand *et al.* (2011)[41]	Europe (France)	Overweight; M 56 ± 4·8	Cross-over	27·4 ± 1·4	23/23	<5·6	4 weeks	Orange 500, 45	Sugar bev	FBG, FBI, S	Yes
Ravn-Haren *et al.* (2013)[34]	Europe (Denmark)	Healthy; M/F 36·2 ± 17·9	Cross-over	22·3 ± 2·6	23/23	<5·6	4 weeks	Apple (clear) 500, 63	No beverage	FBI, S	No
Shidfar *et al.* (2012)[22]	Asia (Iran)	T2D; M 54·8 ± 9·1	Parallel	28·8 ± 3·9	29/29	≥5·6	12 weeks	Cranberry 240, about 31 (estimated)	Sugar-free bev	FBG, P	No
Silver *et al.* (2011)[42]	North America (USA)	Obese; M/F Test: 39·8 ± 8·4 Control: 38·7 ± 8·8	Parallel	Test: 35·2 ± 3·1 Control: 35·7 ± 3·5	22/23	<5·6	12 weeks	Grapefruit (white) about 360 (estimated), about 28 (estimated)	Sugar-free bev	FBG/FBI/ HOMA-IR, S	Yes
Simpson *et al.*2016[44]	Europe (UK)	Overweight/obese, hypercholesterolaemic; M Test: 48·3 ± 3·9 Control: 48·9 ± 4·3	Parallel	Test: 29·9 ± 2·3 Control: 29·3 ± 1·7	18/18	<5·6	12 weeks	Orange 250, 22	Sugar bev	HOMA-IR, S	Yes
Sohrab *et al.* (2014, 2015)[28,32]	Asia (Iran)	T2D; M/F Test: 55 ± 6·7 Control: 56·9 ± 6·8	Parallel	Test: 29·4 ± 3·9 Control: 28·6 ± 4·2	22/22	≥5·6	12 weeks	Pomegranate 250, 24	Sugar bev	FBG/FBI/ HOMA-IR/ HbA1c, S	No

Sumner *et al.* (2005)[45]	North America (USA)	CHD; M/F Test: 69 ± 11 Control: 69 ± 9	Parallel	Test: 28 ± 6 Control: 29 ± 5	25/18	≥5·6	3 months	Pomegranate 240, about 32 (estimated)	Sugar bev	FBG/HbA1c, S	Yes
Tjelle *et al.* (2015)[23]	Europe (Norway)	HTN/pre-HTN; M/F Test: 61 ± 6 Control: 62 ± 6	Parallel	Test: 26 ± 3 Control: 26 ± 3	47/43	<5·6	12 weeks	Blend (red grape, chokeberry, cherry, bilberry) 500, 66	Sugar bev	FBG, S	Yes
Tsang *et al.* (2012)[43]	Europe (UK)	Overweight/obese; M/F 50·4 ± 6·1	Cross-over	26·8 ± 3·3	28/28	<5·6	4 weeks	Pomegranate 500, about 66 (estimated)	Sugar bev	FBG/FBI/ HOMA-IR, P	Yes

M, male; F, female; FBG, fasting blood glucose; FBI, fasting blood insulin; HbA1c, glycosylated Hb; P, primary; COPD, chronic obstructive pulmonary disease; sugar-free bev, beverage without carbohydrate or sugar and/or energy; S, secondary; HOMA-IR, homeostatic model assessment of insulin resistance; HTN, hypertension; sugar bev, beverage matched for carbohydrate or sugar and/or energy; NAFLD, non-alcoholic fatty liver disease; MCI, mild cognitive impairment; T2D, type 2 diabetes.

* Duration = length of dietary intervention for each test or control period.

† When not reported, the amount of sugar provided by the test product was estimated using data from the United States Department of Agriculture National Nutrient Database for the specific type of fruit juice tested[31].

‡ Industry funding includes financial support and/or test products.

§ Juice volume calculated assuming mean body weight of study participants.

intervention (as reported in the original studies for the meta-regression analysis, and categorised as 2–7 weeks, ≥8 weeks in the stratified analysis), baseline fasting blood glucose (<5·6 mmol/l, ≥5·6 mmol/l), location of study (North America, Europe, Asia), study design (parallel, cross-over), outcome (primary, secondary) and Jadad quality score (<4, ≥4). Industry funding (with or without) was also examined in the stratified analysis. Multivariate meta-regressions including all factors with statistically significant ($P < 0{\cdot}05$) regression coefficients were planned for subsequent analyses.

Publication bias was assessed for outcomes with more than ten studies by visual examination of funnel plots of the standard error of the mean difference *v.* the mean difference and the Egger's regression asymmetry test[30]. Sensitivity analyses to explore the influence of a single study on each meta-analysis were conducted by computing the meta-analysis estimates, omitting one study at a time. Level of significance was defined as $P < 0{\cdot}05$. All statistical analyses were completed with STATA, version 12.1 (StataCorp LLC).

Results

Literature search, study characteristics

A total of eighteen RCT of 100 % fruit juice were eligible for inclusion in the present review (Fig. 1). Characteristics of the eighteen RCT of 100 % fruit juice and measures of glucose control or insulin sensitivity included in the meta-analysis are presented in Table 1[31]. Two publications provided relevant outcomes from the same clinical trial and results from both publications were captured for the analysis[28,32]. In two of the identified studies, results of two comparisons of potential interest were presented[33,34], though in order to avoid double-counting of studies, one comparison from each was selected for inclusion in the meta-analysis[33]. In a parallel-design study of the effects of Concord grape juice, the energy-matched control beverage (*v.* a no-beverage control) was selected for the control group[33]. In a cross-over study providing clear or cloudy apple juice within two of the five study arms[34], clear apple juice was selected for the test group as this type of juice is assumed to be more commonly consumed.

Sixteen of the eighteen included trials reported data for fasting blood glucose[20–23,28,32,33,35–43], eleven reported fasting blood insulin[21,28,34–37,39–43], seven reported HOMA-IR[28,36,37,39,42–44] and three reported HbA1c[28,35,45]. Duration of supplementation ranged from 2 weeks to 6 months, with the majority of studies providing the intervention for a period of 8 weeks or more. The studies were predominantly conducted in Europe (*n* 8) or North America (*n* 7), with the remaining three studies conducted in Asia (*n* 3).

All but five studies included a test and control arm; four studies included three arms[23,33,41,42] and one study included five arms[34]. Although all studies were controlled, the type of control beverage provided varied across studies. Across the eighteen studies, twelve indicated some level of industry funding including financial support and/or test products.

Six studies had a Jadad score of ≥4[23,28,32,33,37,39,45], while the remaining trials (twelve of eighteen) had a Jadad score of

Table 2. Jadad scores of study quality and major sources of potential bias by study

Reference	Randomised		Doubled-blind		Withdrawals and dropouts		Major sources of potential bias
	Yes/no*	Method†	Yes/no*	Method†	Description	Cumulative Jadad score	
Banini *et al.* (2006)[35]	1	0	0	0	0	1	Unclear risk of selection bias, attrition bias; high risk of performance bias
Cerdá *et al.* (2006)[20]	1	0	1	1	0	3	Unclear risk of selection bias, attrition bias
Codoñer-Franch *et al.* (2010)[36]	1	0	0	0	0	1	Unclear risk of selection bias, attrition bias; high risk of performance bias
Dohadwala *et al.* (2010)[37]	1	1	1	1	1	5	High risk of attrition bias – 23 % of subjects withdrew from the study
González-Ortiz *et al.* (2011)[21]	1	0	1	0	1	3	Unclear risk of selection bias, performance bias
Guo *et al.* (2014)[38]	1	0	1	0	1	3	Unclear risk of selection bias, performance bias
Habauzit *et al.* (2015)[39]	1	0	1	1	1	4	Unclear risk of selection bias
Hollis *et al.* (2009)[33]	1	0	1	1	1	4	Unclear risk of selection bias
Krikorian *et al.* (2012)[40]	1	0	1	1	0	3	Unclear risk of selection bias, attrition bias
Morand *et al.* (2011)[41]	1	1	0	0	1	3	High risk of performance bias
Ravn-Haren *et al.* (2013)[34]	1	0	0	0	1	2	Unclear risk of selection bias; high risk of performance bias; high risk of attrition bias – 32% of enrolled subjects dropped out before completing all treatments; unclear risk of study design bias – unspecified washout period between treatments
Shidfar *et al.* (2012)[22]	1	0	1	0	1	3	Unclear risk of selection bias, performance bias
Silver *et al.* (2011)[42]	1	1	0	0	1	3	High risk of performance bias; high risk of attrition bias – 20 % of study subjects dropped out between study weeks 6 and 9
Simpson *et al.* (2016)[44]	1	1	0	0	1	3	High risk of performance bias
Sohrab *et al.* (2014, 2015)[28,32]	1	0	1	1	1	4	Unclear risk of selection bias
Sumner *et al.* (2005)[45]	1	1	1	1	1	5	–
Tjelle *et al.* (2015)[23]	1	0	1	1	1	4	Unclear risk of selection bias
Tsang *et al.* (2012)[43]	1	0	0	0	1	2	Unclear risk of selection bias; high risk of performance bias

* Yes, 1; no, 0.
† Appropriate, 1; inappropriate, −1; not specified, 0.

<4. As shown in Table 2, each study was identified by the investigators as a randomised study, though only five provided the methods of random sequence generation. Eleven of the studies were reported to be double-blind, and eight of these detailed a method regarded as appropriate within the Jadad criteria. The remaining eight studies were open label or single blind. Descriptions of study withdrawals, including both the number and reason, were provided in fourteen of the eighteen studies. No studies described inappropriate randomisation or double-blinding methods. High risk for attrition bias was identified in three studies and a cross-over study with an unspecified washout period between treatments presented unclear risk for bias.

Effect of 100 % fruit juice on fasting blood glucose

In the meta-analysis of fasting blood glucose data reported in sixteen RCT, consumption of 100 % fruit juice had no significant effect on fasting blood glucose compared with the control treatment (−0·13 (95 % CI −0·28, 0·01) mmol/l; $P = 0·07$) (Fig. 2); there was moderate to high heterogeneity among the studies ($P < 0·01$, $I^2 = 70·6$). Stratified analyses (Table 3) used to evaluate potential sources of heterogeneity resulted in mean difference estimates ranging from −0·70 to 0·20. Associations that were statistically significant in stratified analyses included an intervention of 2–7 weeks (−0·20 (95 % CI −0·38, −0·08) mmol/l; $P = 0·03$, $I^2 = 57·0$), and studies with a Jadad score of <4 (−0·23 (95 % CI −0·43, −0·03) mmol/l; $P = 0·03$, $I^2 = 74·8$); in both of these stratified analyses, fasting blood glucose was lowered by consumption of 100 % fruit juice compared with the control group. The only factor with a statistically significant regression coefficient in the univariate meta-regressions was study location; therefore no multivariate meta-regression analyses were conducted.

Effect of 100 % fruit juice on fasting blood insulin

Compared with the control treatment, consumption of 100 % fruit juice had no significant effect on fasting blood insulin (−0·24 (95 % CI −3·54, 3·05) pmol/l; $P = 0·89$) with no heterogeneity ($P = 0·52$, $I^2 = 0$) in the eleven RCT included in the analysis (Fig. 3). Stratified analyses of the effects of 100 % fruit juice on fasting blood insulin resulted in mean difference estimates ranging from −8·50 to 11·6, none of which was statistically significant (Table 4).

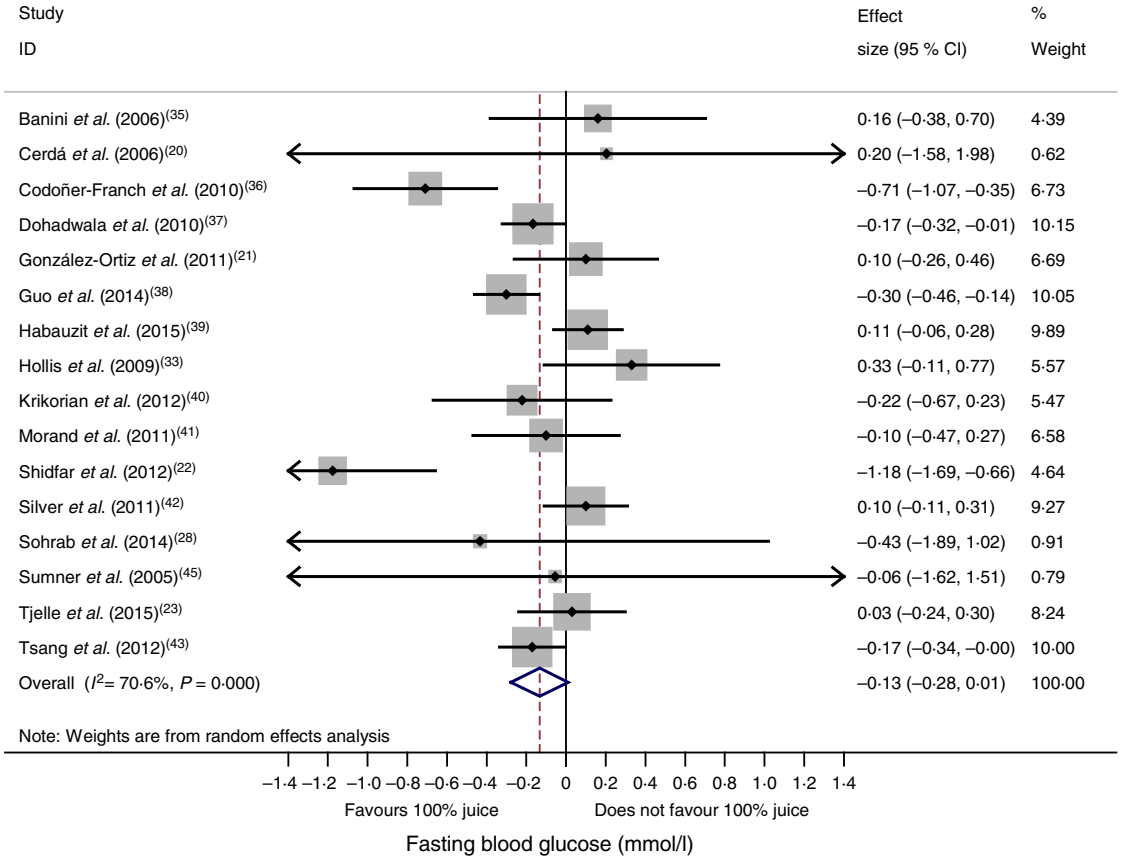

Fig. 2. Meta-analysis of the effects of 100 % fruit juice on fasting blood glucose. Square values represent the mean difference of fasting blood glucose values (mmol/l) based on a random-effects model; 95 % confidence intervals are represented by horizontal lines. Square size is proportional to the weight of each study. The diamond represents the pooled estimate of mean differences ($P = 0{\cdot}07$).

Effect of 100 % fruit juice on insulin resistance

The effect of 100 % fruit juice on HOMA-IR was not significant (−0·22 (95 % CI −0·50, 0·06); $P = 0{\cdot}13$) with moderate to high heterogeneity ($P < 0{\cdot}01$, $I^2 = 73{\cdot}9$) (Fig. 4). Stratified analyses resulted in mean difference estimates ranging from −1·60 to 0·50 (Table 5). In stratified analyses, HOMA-IR was significantly lower in the 100 % fruit juice groups compared with the control group in studies in which pomegranate juice was consumed (−0·37 (95 % CI −0·57, −0·18); $P < 0{\cdot}005$, $I^2 = 0$) or intervention duration was 2–7 weeks (−0·41 (95 % CI −0·59, −0·23); $P < 0{\cdot}005$, $I^2 = 0$). In the univariate meta-regressions, only volume of juice intervention showed a statistically significant inverse association with change in HOMA-IR (regression coefficient = −0·002; $P = 0{\cdot}01$).

Effect of 100 % fruit juice on glycosylated Hb

The effect of 100 % fruit juice on HbA1c was not significant (−0·001 (95 % CI −0·38, 0·38) %; $P > 0{\cdot}99$) with low heterogeneity ($P < 0{\cdot}01$, $I^2 = 22{\cdot}3$) (Fig. 5). Stratified analyses resulted in mean difference estimates ranging from −0·11 to 0·60 (Table 6). No statistically significant associations were observed in the stratified analyses or univariate meta-regressions.

Publication bias

The potential for publication bias was investigated through visual inspection of funnel plots for analyses with a sufficient number of studies, namely fasting blood glucose and fasting blood insulin. Visual inspection of funnel plots for fasting blood glucose showed that all but three studies[22,36,38] fell inside the funnel. These three studies had relatively smaller mean difference estimates indicative of statistically significant beneficial effects of the intervention beverages. Sensitivity analyses in which each study was removed from the analysis individually or all three simultaneously resulted in a mean difference that was still negative and not significantly different from zero (data not shown), thus suggesting no publication bias. Results from the Egger's test supported this conclusion for both fasting blood glucose and insulin (Fig. 6; $P = 0{\cdot}80$ and 0·38, respectively).

Sensitivity analysis

Sensitivity analyses that excluded individual RCT resulted in estimates similar to values derived from all studies, although some mean differences became statistically significant. In the case of fasting blood glucose, omission of either of three studies[33,39,42] resulted in overall mean difference estimates that were statistically significant and indicative of a beneficial effect of 100 % fruit juice consumption (mean difference of −0·16; 95 % CI −0·31, −0·005). The effects of 100 % fruit juice on fasting blood insulin or HOMA-IR were not found to be sensitive to any particular study included in the meta-analysis. The sensitivity analysis conducted for fasting blood insulin assuming

Table 3. Stratified analyses of effects of 100 % fruit juice on fasting blood glucose (FBG)

Parameter	Studies (*n*)	Net change	95 % CI	Overall *P*	Test of heterogeneity		Unadjusted (univariate) meta-regression		
					P	I^2 (%)	RC	SE	*P*
All studies	16	−0·13	−0·28, 0·01	0·07	<0·005	70·6			
Fruit juice type									
Apple	–	–	–	–	–	–	–	–	–
Berry	2	−0·70	−1·56, 0·15	0·11	<0·005	90·0	−0·56	0·32	0·11
Blend	1	0·03	−0·24, 0·30	0·83	–	–	0·10	0·39	0·81
Citrus	4	−0·12	−0·43, 0·19	0·45	<0·005	83·1	−0·06	0·27	0·84
Grape	4	−0·03	−0·28, 0·22	0·83	0·14	45·9	0·07	0·28	0·82
Pomegranate	5	−0·12	−0·27, 0·03	0·10	0·72	0	Reference	–	–
Control group									
Sugar bev	10	−0·09	−0·21, 0·03	0·14	0·04	49·6	0·26	0·29	0·39
Sugar-free bev	4	−0·24	−0·84, 0·36	0·43	<0·005	85·6	0·13	0·34	0·71
No beverage	2	−0·30	−1·15, 0·55	0·49	0·01	85·5	Reference	–	–
Volume of juice							<0·005	<0·005	0·75
≤250 ml/d	5	−0·29	−0·93, 0·36	0·38	<0·005	77·9	–	–	–
>250 ml/d	11	−0·11	−0·25, 0·03	0·13	<0·005	69·1	–	–	–
Duration							0·01	0·01	0·44
2–7 weeks	7	−0·20	−0·38, −0·02	0·03	0·03	57·0	–	–	–-
≥8 weeks	9	−0·09	−0·30, 0·12	0·39	<0·005	72·9	–	–	–
Baseline FBG									
<5·6 mmol/l	11	−0·08	−0·21, 0·06	0·28	<0·005	70·7	Reference	–	–
≥5·6 mmol/l	5	−0·51	−1·10, 0·09	0·10	0·07	54·3	−0·49	0·23	0·06
Location									
Asia	3	−0·65	−1·36, 0·05	0·07	0·01	80·0	Reference	–	–
Europe	6	−0·14	−0·36, 0·09	0·24	<0·005	72·8	0·45	0·24	0·08
North America	7	0·01	−0·15, 0·16	0·94	0·19	31·0	0·62	0·24	0·02
Outcome									
Primary	4	−0·25	−0·70, 0·20	0·27	<0·005	83·4	Reference	–	–
Secondary	12	−0·10	−0·26, 0·05	0·20	<0·005	65·6	0·14	0·21	0·53
Study design									
Cross-over	5	−0·13	−0·28, 0·02	0·08	0·02	66·9	0·02	0·19	0·91
Parallel	11	−0·15	−0·43, 0·12	0·27	<0·005	73·9	Reference	–	–
Jadad score									
<4	10	−0·23	−0·43, -0·03	0·03	<0·005	74·8	Reference	–	–
≥4	6	0·02	−0·15, 0·18	0·86	0·13	40·9	0·26	0·18	0·17
Study funding									
Industry support	11	−0·07	−0·21, 0·07	0·34	<0·005	62·5	0·30	0·20	0·17
No industry support	5	−0·38	−0·84, 0·08	0·11	<0·005	75·1	Reference	–	–

RC, regression coefficient; sugar bev, beverage matched for carbohydrate or sugar and/or energy; sugar-free bev, beverage with non-energy-containing or no added sweetener.

a correlation coefficient of 0·7 in the derivation of the pooled variance for cross-over studies showed no significant effect of 100 % fruit juice on fasting blood insulin (results not shown).

Discussion

The present systematic review and meta-analysis provides a comprehensive, quantitative assessment of the relationship between 100 % fruit juice and measures of glycaemic control. Results from this meta-analysis of eighteen RCT show no significant effect of 100 % fruit juice on fasting blood glucose, fasting blood insulin, insulin resistance as evaluated by HOMA-IR or HbA1c. Additionally, results of stratified analyses confirm the lack of consistent associations between 100 % fruit juice consumption and these markers for diabetes. The absence of any clear adverse or beneficial effect of 100 % fruit juice on markers of diabetes in the present meta-analysis of available RCT suggests a largely neutral role of 100 % fruit juice on glucose–insulin homeostasis.

The findings of the present meta-analysis are generally consistent with a 2014 meta-analysis by Wang *et al.*[12]. Overall, seven studies were included in both the previous and the present meta-analysis[20,21,33,35,37,41,45]. The eleven additional trials included in the present analysis reflect recent additions to the literature as well as studies not captured by Wang *et al.* [12]. As in the present analysis, no significant effect on glycaemic control measured by fasting glucose, fasting insulin or HbA1c was reported in the meta-analysis of studies identified as 100 % fruit juice by Wang *et al.*[12]. In contrast to the present analysis in which no effect of 100 % fruit juice on HOMA-IR was found, a significant increase in HOMA-IR was reported by Wang *et al.*[12] based on data from three trials, only one of which was considered eligible for the present meta-analysis[45]. The other two HOMA-IR values in the meta-analysis by Wang *et al.*[12] include a value from a study not meeting our inclusion criteria[16], and a value attributed to the trial by Sumner *et al.*[45] which was neither reported in that paper nor noted as sourced from the study authors. The value attributed to Sumner accounted for 78 % of the weighted mean HOMA-IR in the meta-analysis by Wang *et al.*[12], and therefore largely explains the difference between the previous and present analyses. Findings from the present meta-analysis of RCT on markers

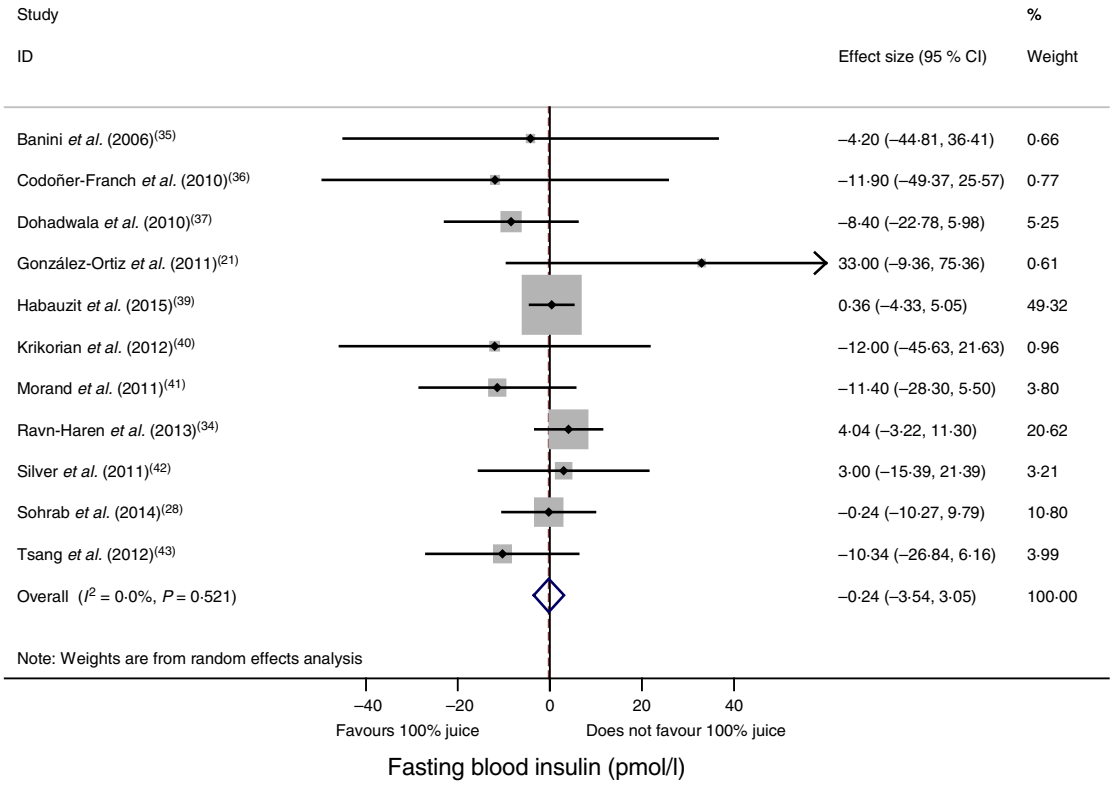

Fig. 3. Meta-analysis of the effects of 100 % fruit juice on fasting blood insulin. Square values represent the mean difference of fasting blood insulin values (pmol/l) based on a random-effects model; 95 % confidence intervals are represented by horizontal lines. Square size is proportional to the weight of each study. The diamond represents the pooled estimate of mean differences ($P = 0{\cdot}89$).

for diabetes are also consistent with findings from a meta-analysis of prospective cohorts showing that consumption of 100 % fruit juice is not associated with increased risk of T2D[46] and findings from a more recent meta-analysis of cohorts in which diabetes was clinically verified[11].

Stratified analyses were conducted as part of the present meta-analysis to investigate specific conditions that may adversely or beneficially affect glucose–insulin homeostasis. The stratifications included parameters to differentiate among the juice intervention, study population and study characteristics. Consistent with the primary findings, results from the stratified analyses showed no significant effect of 100 % fruit juice on fasting blood insulin and HbA1c, though results of both analyses, and in particular HbA1c, were limited by the small number of studies. Stratified analyses of fasting blood glucose showed a significantly greater reduction from baseline with 100 % fruit juice compared with the control in trials with an intervention duration of 2–7 weeks and trials with a Jadad score <4. The significant effect observed in shorter studies could reflect higher compliance by study participants over a shorter study intervention. However, a cross-tabulation of the studies with fasting blood glucose data by these two factors reveals that all studies with a shorter duration of intervention (2–7 weeks) also had a Jadad score <4, which is an indicator of a lower methodological quality trial. As detailed in the review of Jadad scores by studies (Table 2), many of the RCT suggesting a beneficial effect of 100 % fruit juice on fasting blood glucose had one or more major sources of potential bias, and in particular high or unclear performance bias. Findings in the stratified analyses therefore provide some though limited support for a beneficial effect of fruit juice on fasting blood glucose. Stratified analyses of HOMA-IR also showed a significantly greater reduction from baseline with 100 % fruit juice compared with the control in trials with an intervention duration of 2–7 weeks, and additionally in trials with pomegranate juice. The significance of these findings also is limited, as each analysis was based on data from only two studies and did not notably reduce heterogeneity. The inverse association of volume of 100 % fruit juice with HOMA-IR identified in univariate meta-regressions also is an indicator of potentially beneficial effects of 100 % fruit juice, albeit very small as evidenced by the relatively small regression coefficient.

A variety of juices was provided as test beverages across the studies and the types and concentrations of some bioactives in fruit juice vary across fruit juice type. For example, pomegranate juice is a unique source of ellagitannins, including punicalagins[47]. Among citrus juices, grapefruit juice is a concentrated source of naringin while the primary flavonoid in orange juice is hesperidin[48,49]. Cranberries are a source of polyphenols including procyanidins, anthocyanins, quercetin and myricitrin[50], the primary anthocyanins in many grape juices are glucosides of cyanidin or delphinidin[49,51], and apple juice is a source of quercetin[49,51]. The amount of fruit juice consumed during the dietary interventions was also highly variable, with juice intake of approximately two cups or more (480 to 595 ml) per d in nine of the interventions and one cup or less in six studies (<250 ml). The amount of sugars provided by the juices ranged from 22 to 97 g. The

Table 4. Stratified analyses of effects of 100 % fruit juice on fasting blood insulin

Parameter	Studies (*n*)	Net change	95 % CI	Overall *P*	Test of heterogeneity *P*	Test of heterogeneity I^2 (%)	Unadjusted (univariate) meta-regression RC	SE	*P*
All studies	11	−0·24	−3·54, 3·05	0·89	0·52	0			
Fruit juice type									
Apple	1	4·04	−3·22, 11·3	0·28	.	–	5·59	5·66	0·36
Berry	–	–	–	–	–	–	–	–	–
Blend	–	–	–	–	–	–	–	–	–
Citrus	4	−0·44	−4·80, 3·92	0·84	0·53	0	1·11	4·83	0·83
Grape	3	−8·50	−21·07, 4·07	0·19	0·96	0	−6·95	7·71	0·40
Pomegranate	3	−0·72	−14·90, 13·46	0·92	0·16	46·1	Reference	–	–
Control group									
Sugar bev	6	−1·69	−5·52, 2·14	0·39	0·50	0	−5·52	4·78	0·28
Sugar-free bev	2	11·68	−14·98, 38·34	0·39	0·20	38·3	4·95	9·73	0·63
No beverage	3	3·24	−3·78, 10·25	0·37	0·67	0	Reference	–	–
Volume of juice							−0·02	0·02	0·26
≤250 ml/d	3	2·66	−11·29, 16·61	0·71	0·32	13·5	–	–	–
>250 ml/d	8	−0·44	−3·96, 3·07	0·81	0·46	0	–	–	–
Duration							0·09	0·24	0·73
2–7 weeks	6	−2·13	−11·60, 7·35	0·66	0·21	30·6	–	–	–
≥8 weeks	5	−0·44	−4·40, 3·51	0·83	0·76	0	–	–	–
Baseline FBG									
<5·6 mmol/l	9	−0·41	−4·48, 3·66	0·84	0·37	7·4	Reference	–	–
≥5·6 mmol/l	2	−1·20	−10·81, 8·41	0·81	0·51	0	−1·09	5·24	0·84
Location									
Asia	1	−0·24	−10·27, 9·79	0·96	–	–	Reference	–	–
Europe	5	−0·43	−5·24, 4·38	0·86	0·30	17·6	0·33	5·74	0·96
North America	5	−2·70	−12·78, 7·39	0·60	0·41	0	−2·45	7·63	0·76
Outcome									
Primary	3	0·73	−23·20, 24·65	0·95	0·17	42·7	Reference	–	–
Secondary	8	0	−3·39, 3·39	1·00	0·63	0	4·58	7·54	0·56
Study design									
Cross-over	5	−1·41	−6·58, 3·76	0·59	0·22	30·4	−0·54	4·50	0·91
Parallel	6	0·21	−7·78, 8·20	0·96	0·65	0	Reference	–	–
Jadad score									
<4	8	−0·89	−7·60, 5·81	0·79	0·35	10·2	Reference	–	–
≥4	3	−0·44	−4·52, 3·63	0·83	0·53	0	−0·48	3·86	0·90
Study funding									
Industry support	8	−1·84	−5·83, 2·16	0·37	0·68	0	−6·13	4·31	0·19
No industry support	3	3·20	−3·78, 10·19	0·37	0·30	16·8	Reference	–	–

RC, regression coefficient; sugar bev, beverage matched for carbohydrate or sugar and/or energy; sugar-free bev, beverage with non-energy-containing or no added sweetener; FBG, fasting blood glucose.

'100 % fruit juice' category therefore represents a heterogeneous food group and differences in the type and composition of fruit juices may be important when considering the physiological effects of fruit juice, including effects on glycaemic control and insulin sensitivity. Stratified analyses, however, showed no clear differences across categorisations and heterogeneity was not notably reduced.

The RCT of 100 % fruit juices identified in the present review also used a variety of control products, including energy-containing beverages matched for sugar or carbohydrate content, sugar-free beverages containing non-energy-containing sweeteners or only water, and, in some studies, no beverage. Peluso & Palmery[52] have noted that selection of an appropriate placebo in studies of the postprandial response to fruit juice is critical, with energy and sugar-matched beverages (including proportions of glucose and fructose) providing an appropriate control to assess the effects of bioactives in juice, and a water beverage providing an appropriate control to assess the effects of juice as a whole[52]. Stratified analyses of fasting blood glucose by these control group comparisons did not result in significant effects, suggesting that neither the non-sugar juice components nor the juice itself had an effect on fasting blood glucose in the clinical trials.

The effects of 100 % fruit juice on measures of glucose control or insulin sensitivity varied little across study population characteristics including baseline fasting blood glucose levels. Body weight status of study participants is another important characteristic as overweight and obesity are recognised risk factors for the development of T2D due to decreased sensitivity of non-adipose tissue to insulin[2]. In all but one of the studies with reported BMI data[34], mean BMI exceeded 25 kg/m^2, indicating that the study populations were generally overweight or obese individuals. The available reported data on body weight or BMI indicate no differences in change between the juice intervention and control groups. In addition to weight status, the study populations also represented a variety of health states including healthy, diabetic, hypertensive/pre-hypertensive, hypercholesterolaemic, and adults with various other conditions. While many of these conditions are common co-morbidities of overweight and obesity, it is difficult to

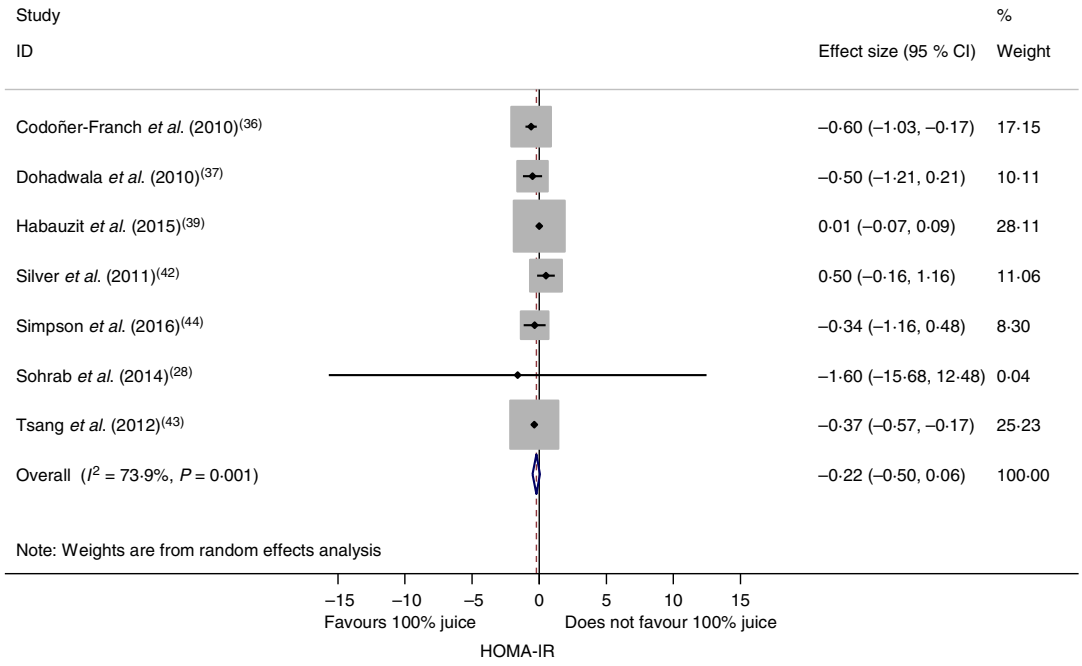

Fig. 4. Meta-analysis of the effects of 100 % fruit juice on the homeostatic model assessment of insulin resistance (HOMA-IR). Square values represent the mean difference of the HOMA-IR index based on a random-effects model; 95 % confidence intervals are represented by horizontal lines. Square size is proportional to the weight of each study. The diamond represents the pooled estimate of mean differences ($P = 0{\cdot}13$).

delineate their independent role in the relationship between 100 % fruit juice consumption and diabetes risk.

Many methods are used to assess bias in RCT when conducting a meta-analysis, including the Jadad criteria[53]. Based on the Jadad criteria, which reflect randomisation, double blinding, and recording of withdrawals and dropouts[19], the majority of studies in this meta-analysis had an unclear risk of selection bias due to absence of a description of the random sequence generation. A relatively high proportion of studies were non-double-blind (seven of eighteen) which points to a high risk of performance bias. Regarding attrition bias, the majority of studies (fourteen of eighteen) provided information on participant disposition throughout the study and the data largely indicate low risk of bias, though attrition was relatively high (20–32 %) in three studies[34,37,42] and the remaining studies have unknown or potentially high risk for this source of bias. Other potential sources of bias not captured in the Jadad criteria but noted upon review of the studies include unknown or potentially high bias due to an unspecified washout period between interventions[34].

Despite concerns that 100 % fruit juice may have adverse effects on glycaemic control, primarily as a result of sugars in these beverages, results from this analysis of RCT do not support a conclusion that 100 % fruit juice adversely affects glucose–insulin homeostasis. The results largely indicate no effect on glycaemic control. Some stratified analyses suggest the possibility of a beneficial effect of 100 % fruit juice on fasting blood glucose and HOMA-IR, though the evidence is inconclusive based on limitations of the available data. A mechanism by which 100 % fruit juice may have a favourable effect on measures of glycaemic control is not clearly known, though some evidence, largely from *in vitro* and animal studies, indicates that polyphenols may favourably affect glucose–insulin homeostasis through a variety of mechanisms including inhibition of glucose absorption, stimulation of insulin secretion from the pancreas and change in glucose release from the liver, activation of insulin receptors and glucose uptake by cells, and modulation of cell signalling pathways and gene expression[10]. Further research is needed to understand these effects.

A strength of the present meta-analysis is the large number of randomised, controlled clinical trials identified for inclusion in the quantitative analysis. The broad though focused search strategy identified studies in which glucose metabolism outcomes were primary outcomes as well as studies in which the measures were collected as secondary outcomes or routine monitoring during the clinical trials. The large number of identified studies allowed for stratified analyses by similar characteristics of the intervention, study population, and overall study design to further explore effects of 100 % fruit juice on diabetes biomarkers. However, sample sizes in many stratified analyses were relatively small, and many analyses may result in detection of spurious associations, therefore these findings must be interpreted with caution.

Although the total number of identified studies was relatively large, variability among some parameters of study interventions, populations, and overall study design are limitations of this analysis and must be considered when interpreting the findings. The included studies reflect a diverse range of juice interventions (both type of juice and amount consumed), intervention durations, variable dietary restrictions throughout the intervention period (and typically no restrictions on consumption of other types of 100 % fruit juice), study populations with a range of health conditions, and studies with potential for some bias. Variability in these factors and potentially other factors not considered in the analysis contribute to the observed heterogeneity among studies, thus making it difficult to conclusively interpret the findings.

Table 5. Stratified analyses of effects of 100 % fruit juice on the homeostatic model assessment of insulin resistance

Parameter	Studies (*n*)	Net change	95 % CI	Overall *P*	Test of heterogeneity *P*	Test of heterogeneity I^2 (%)	Unadjusted (univariate) meta-regression RC	SE	*P*
All studies	7	−0·22	−0·5, 0·06	0·13	<0·005	73·9			
Fruit juice type									
Apple	–	–	–	–	–	–	–	–	–
Berry	–	–	–	–	–	–	–	–	–
Blend	–	–	–	–	–	–	–	–	–
Citrus	4	−0·11	−0·52, 0·29	0·58	0·02	70·8	0·26	0·44	0·58
Grape	1	−0·50	−1·21, 0·21	0·17	–	–	−0·12	0·64	0·86
Pomegranate	2	−0·37	−0·57, −0·18	0·00	0·86	0	Reference	–	–
Control group									
Sugar bev	5	−0·23	−0·53, 0·07	0·14	0·01	71·9	0·38	0·34	0·33
Sugar-free bev	1	0·50	−0·16, 1·16	0·14	–	–	1·10	0·51	0·10
No beverage	1	−0·60	−1·03, −0·17	0·01	–	–	Reference	–	–
Volume of juice							<0·005	<0·005	0·01
≤ 250 ml/d	2	−0·34	−1·17, 0·48	0·41	0·86	0	–	–	–
>250 ml/d	5	−0·21	−0·51, 0·10	0·19	<0·005	82·2	–	–	–
Duration							0·02	0·01	0·08
2–7 weeks	2	−0·41	−0·59, −0·23	0·00	0·35	0	–	–	–
≥8 weeks	5	−0·01	−0·25, 0·23	0·92	0·31	16·9		–	–
Baseline FBG									
<5·6 mmol/l	6	−0·22	−0·50, 0·07	0·14	<0·005	78·2	Reference	–	–
≥5·6 mmol/l	1	−1·60	−15·68, 12·48	0·82	–	–	−1·38	7·36	0·86
Location									
Asia	1	−1·60	−15·68, 12·48	0·82	–	–	Reference	–	–
Europe	4	−0·28	−0·61, 0·04	0·08	<0·005	83·9	1·31	7·31	0·87
North America	2	0·01	−0·97, 0·99	0·99	0·04	75·4	1·62	7·31	0·84
Outcome									
Primary	1	−0·37	−0·57, −0·18	<0·005	–	–	Reference	–	–
Secondary	6	−0·17	−0·52, 0·18	0·34	0·03	58·8	0·20	0·39	0·64
Study design									
Cross-over	3	−0·22	−0·56, 0·12	0·20	<0·005	85·4	−0·05	0·35	0·90
Parallel	4	−0·18	−0·83, 0·48	0·60	0·06	59·9	Reference	–	–
Jadad score									
<4	4	−0·27	−0·64, 0·10	0·16	0·05	60·8	Reference	–	–
≥4	3	0	−0·08, 0·09	0·95	0·37	0	0·11	0·34	0·75
Study funding									
Industry support	6	−0·22	−0·50, 0·07	0·14	<0·005	78·2	1·38	7·36	0·86
No industry support	1	−1·60	−15·68, 12·48	0·82	–	–	Reference	–	–

RC, regression coefficient; sugar bev, beverage matched for carbohydrate or sugar and/or energy; sugar-free bev, beverage with non-energy-containing or no added sweetener; FBG, fasting blood glucose.

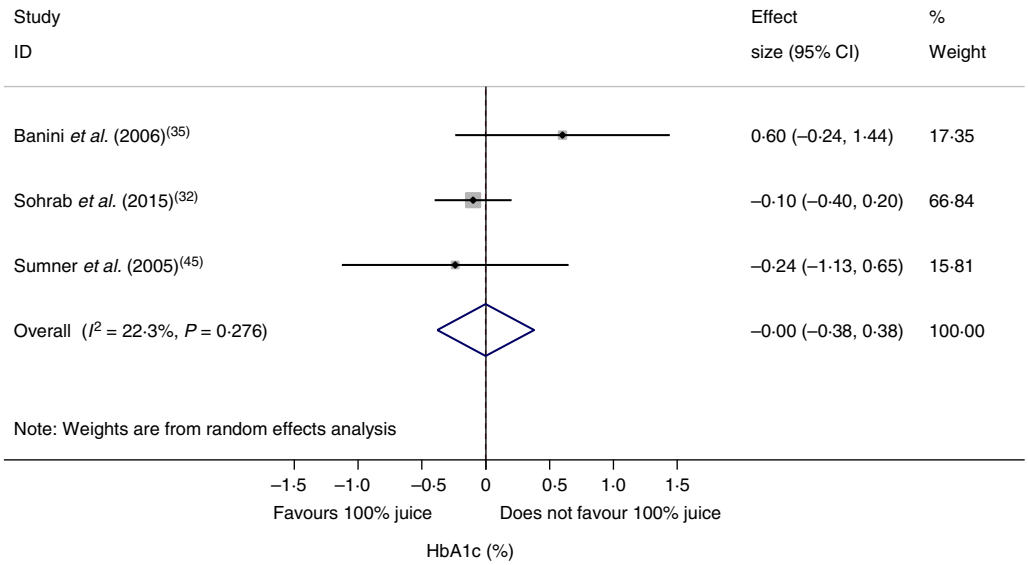

Fig. 5. Meta-analysis of the effects of 100 % fruit juice on glycosylated Hb (HbA1c; %). Square values represent the mean difference of HbA1c values based on a random-effects model; 95 % confidence intervals are represented by horizontal lines. Square size is proportional to the weight of each study. The diamond represents the pooled estimate of mean differences ($P = 1·00$).

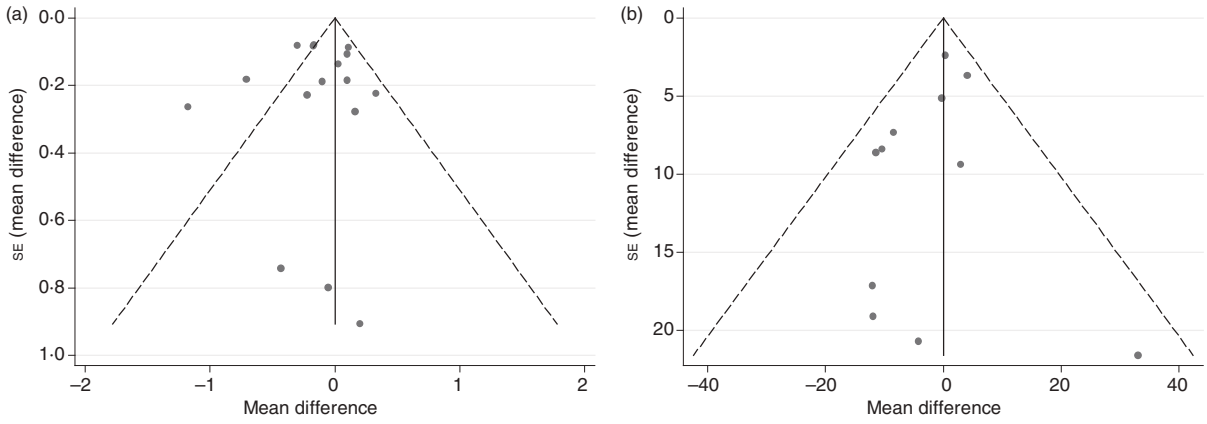

Fig. 6. Funnel plots with pseudo 95 % confidence limits for detection of publication bias among randomised controlled trials examining fasting blood glucose (a) and fasting blood insulin (b). For fasting blood glucose, *P* value for Egger's test = 0·80. For fasting blood insulin, *P* value for Egger's test = 0·38.

Conclusion

In conclusion, the available RCT indicate that repeated intake of 100 % fruit juice does not have a significant effect on glycaemic control or measures of insulin resistance. These findings from RCT of markers for diabetes are consistent with findings from some observational studies suggesting that consumption of 100 % fruit juice is neutral regarding

Table 6. Stratified analyses of effects of 100 % fruit juice on glycosylated Hb (%)

Parameter	Studies (*n*)	Net change	95 % CI	Overall *P*	Test of heterogeneity *P*	Test of heterogeneity I^2 (%)	Unadjusted (univariate) meta-regression RC	SE	*P*
All studies	3	−0·001	−0·38, 0·38	1·00	0·28	22·3	–	–	–
Fruit juice type									
Apple	–	–	–	–	–	–	–	–	–
Berry	–	–	–	–	–	–	–	–	–
Blend	–	–	–	–	–	–	–	–	–
Citrus	–	–	–	–	–	–	–	–	–
Grape	1	0·60	−0·24, 1·44	0·16	–	–	0·71	0·45	0·36
Pomegranate	2	−0·11	−0·40, 0·17	0·43	0·77	0	Reference	–	–
Control group									
Sugar bev	2	−0·11	−0·40, 0·17	0·43	0·77	0	−0·71	0·45	0·36
Sugar-free bev	–	–	–	–	–	–	–	–	–
No beverage	1	0·60	−0·24, 1·44	0·16	–	–	Reference	–	–
Volume of juice							−0·01	0·01	0·37
≤250 ml/d	3	0	−0·38, 0·38	1·00	0·28	22·3	–	–	–
>250 ml/d	–	–	–	–	–	–			
Duration							−0·09	0·06	0·36
2–7 weeks	1	0·60	−0·24, 1·44	0·16	–	–	–	–	–
≥8 weeks	2	−0·11	−0·40, 0·17	0·43	0·77	0	–	–	–
Baseline FBG									
<5·6 mmol/l	1	0·60	−0·24, 1·44	0·16	–	–	Reference	–	–
≥5·6 mmol/l	2	−0·11	−0·40, 0·17	0·43	0·77	0	−0·71	0·45	0·36
Location									
Asia	1	−0·10	−0·40, 0·20	0·52	–	–	Reference	–	–
Europe	–	–	–	–	–	–	–	–	–
North America	2	0·19	−0·63, 1·02	0·65	0·18	44·8	0·29	0·60	0·71
Outcome									
Primary	1	0·60	−0·24, 1·44	0·16	–	–	Reference	–	–
Secondary	2	−0·11	−0·40, 0·17	0·43	0·77	0	−0·71	0·45	0·36
Study design									
Cross-over	–	–	–	–	–	–	–	–	–
Parallel	3	0	−0·38, 0·38	1·00	0·28	22·3	Reference	–	–
Jadad score									
<4	1	0·60	−0·24, 1·44	0·16	–	–	Reference	–	–
≥4	2	−0·11	−0·40, 0·17	0·43	0·77	0	−0·71	0·45	0·36
Study funding									
Industry support	2	0·19	−0·63, 1·02	0·65	0·18	44·8	0·29	0·60	0·71
No industry support	1	−0·10	−0·40, 0·20	0·52	–	–	Reference	–	–

RC, regression coefficient; sugar bev, beverage matched for carbohydrate or sugar and/or energy; sugar-free bev, beverage with non-energy-containing or no added sweetener; FBG, fasting blood glucose.

risk of T2D. Results from stratified analyses and univariate meta-regressions also largely showed no significant associations between 100 % fruit juice and these measures of glucose control. High-quality studies of glucose–insulin homeostasis measures monitored in well-defined and controlled populations are needed to further clarify the effects of 100 % fruit juice on diabetes risk as evaluated by these biomarkers. Such research focused on commonly consumed juices served in moderate daily portions reflective of prudent dietary guidance would provide important information to further our understanding of the role of 100 % fruit juice on glycaemic control.

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M. M. M., E. C. B. and L. M. B. designed the study. M. M. M. and E. C. B. completed the literature searches and M. M. M., E. C. B. and K. A. B. completed the data extraction. L. M. B. oversaw all statistical analyses. M. M. M., E. C. B., K. A. B. and L. M. B. contributed to interpretation of the findings. M. M. M. drafted the manuscript. All authors read, critically reviewed, edited and approved the final manuscript. The Juice Products Association developed the research question though had no role in the study design, data collection and analysis, interpretation of the data, or preparation of the manuscript.

The study sponsor reviewed an early draft of the manuscript and provided minor editorial suggestions for consideration by the authors who retained the authority to accept or reject them.

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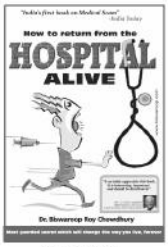

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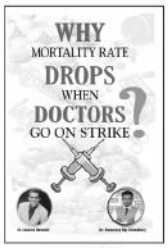

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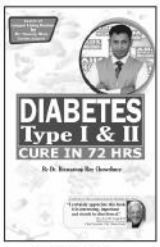

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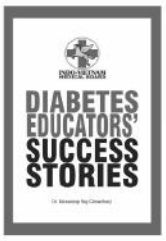

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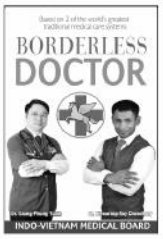

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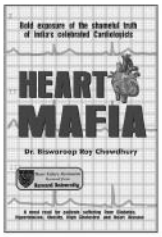

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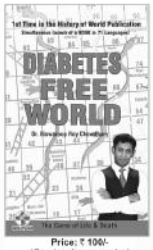

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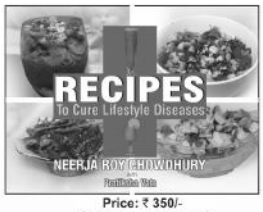

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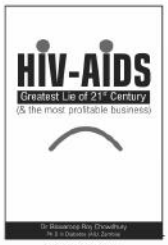

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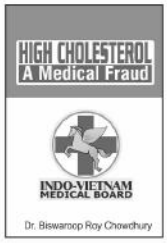

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SECTION - 4

● Diabetes Reversal by Plant-Based Diet

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Diabetes Reversal by Plant-Based Diet

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Abstract

Introduction: Diabetes causes a never-ending medicine and or insulin treatment for the diseased. Also, the patients are bound to follow a particular diet, with eliminating most of the sugary foods; that further deteriorates the quality of life. This gave way to the study, focused on diabetes cure without medicines and on rich fruits and vegetable diet. The clinical trial on 55 diabetes patients with a team of 6 medical associates was practiced for 3- days at Zorba, The Buddha, 10 – Tropical Drive, Ghitorni, New Delhi from 29th April to 1st May, 2016. The goal was to establish and observe the effects of plant-based diet on the sugar levels of the diabetes patients. These included both insulin-dependent and independent, diabetes type-1 and type-2 patients. The 3-days Residential Treatment Tour involved 55 subjects with different age groups and demographic profiles. The study considered participants from different countries to find out the global impact of the treatment.

Objective: The burden of the disease diabetes is rising globally. The aim of the research is to find out that on discontinuing the medicines and being on a particular plant-based diet, can high blood glucose levels in diabetes patients be normalized.

Methodology: Clinical trials were performed on diabetes patients for 3-days continuously. The sample size of the study was n=55 patients. Medicines were eliminated from the first day of the trial. Thereafter, following 3-days, the participants were kept on a prescribed plant-based diet. Both fasting and post-prandial readings were measured each day along with the weights of the participants. The subjects with varying diabetes history, age groups, type of diabetes, insulin dependency and demographic profiles were part of the trial.

Findings of the study: The study reported controlled* blood glucose levels for 84% of patients and partially-controlled* levels for 16% of patients. Those with controlled* levels could attain a healthy blood glucose range without medicines and or insulin, along with the prescribed diet in 3-days. Those with partially controlled* levels could attain a healthy blood glucose range with less than 50% of insulin than prescribed earlier. Among diabetes type-2 patients the study reported 100% results with all the patients maintaining a healthy blood glucose level. While among diabetes type-1 patients, 57% reported controlled* blood glucose levels through the diet and zero-medications. Whereas, 43% reported healthy blood sugar levels through the diet and insulin reduction. In addition of the insulin-dependent group, 59% could completely drop their insulin requirements and 41% could reduce the requirement to at least 50%. The weight reduction for 55 patients in 3-days was reported as 1.14 kgs of average weight loss per individual. Also, the patients had symptomatic relief from general fatigue and weaknesses. The plant-based diet proved to be beneficial with regards to energy and nutritional fulfillments.

Future scope: Diabetes treatment has both health and economic burden on society. With reference to the present research, a new approach for the treatment of this considered life-style metabolic disability can be shaped. The plant-based diet has been found effective to cure and control diabetes, eliminating the medicine or insulin requirements. Further research on the subject matter can present a medicine-free-food-science based treatment for the disease. At the same time, this unique treatment approach will eliminate the risks of medicine side-effects. On the basis of this research, diabetes education can be developed for better understanding of the disease and better living for the diseased population.

Keywords: Plant-based diet; Diabetes; Diabetes type I and type II; Insulin dependent; Blood glucose levels

Introduction

In the latest Clinical Practice Recommendations provided by the American Diabetes Association-ADA, Medical Nutrition Therapy is highly recommended for Diabetes care. However, they could not define a dietary pattern or establish a specific nutrition therapy for delay or prevention of the risk of diabetes. They further suggested increased intake of whole grains, fruits, vegetables and legumes, reducing refined and sugary foods [1]. In addition, intensive life-style changes were reported to be 58% effective after 3 years by the ADA [1].

The Medical Nutrition Therapy for diabetes paved its way through many randomized trials, meta-analysis and observational studies [2]. Improved glycemic and metabolic control were evident with reduction in A1c and blood glucose levels in diabetes patients. The results reported favored both type 1 and 2 population and worked irrespective of disease duration [2]. Moreover, it was also established that life-style interventions work better than metformin in reducing the incidence of type 2 diabetes [3]. The research in hand presents a defined model of managing diabetes with plant-based diet protocol eliminating the need for medications. The study will provide a strong foundation with extensive future scope for research due to its practical implications.

Review of Literature

The correlation between life-style orientations and diseases has

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been profound. The present research is rooted within the vast literature present in support of association between diabetes and diet. Some of the related studies have been listed below.

Glycemic control and diabetes

In the study presented by Riccardi et al. on glycemic control in diabetes, they could establish a deep relationship between pre-diabetes and type 1 and 2 diabetes with high glycemic load. Figure 1 shows the effects of high/low glycemic index (GI) on blood glucose levels in type 1 Diabetes patients, similar results were seen in type 2 diabetes patients (Figure 1).

The glycemic load is explained as glycemic index (GI) of a particular food multiplied by the amount of carbohydrate contained in an average portion of the food consumed [4]. The study supported low GI and high fiber-rich diet to manage post-prandial blood glucose levels in pre-diabetes and diabetes [4].

Studies also reported that glycemic index can be used as an effective marker along with fiber-content and nutritional value to classify carbohydrate rich foods and their preferences in routine diet [5]. This presented relevance in case of diabetes control and prevention. In addition, a comparative study for glycemic index or the quantity of carbohydrates on glycated hemoglobulin, C-reactive proteins, lipids and plasma glucose on type 2 diabetes patients gave positive results [6]. The outcomes of the 1-year controlled trial on 162 type 2 patients managed by sole diet gave the mean C-reactive protein being 30% low in low-GI diet in a comparison to high GI diet. The study reported sustainable reductions in post-prandial glucose level and C-reactive proteins and referred the diet management system to aid in type 2 diabetes management [6].

Animal protein and diabetes

The Singapore Chinese Health Study (SCHS) investigated association between dietary patterns and risk of type 2 diabetes in Chinese men and women in Singapore [7]. The study examined 43,176 individuals aged 47-74 years and diabetes free. The study performed Cox regression for diet pattern scores and risk of type 2 diabetes in individuals [8]. Their dietary patterns showed positive relation between meat-rich foods and risk of type 2 diabetes. Whereas fruits, vegetables and soy-rich foods inversely affected risk of type 2 diabetes [8]. Meat consumption and incidence of type 2 diabetes has been elucidated in a cohort study of 4,366 Dutch participants [9]. This study delivered the effects of processed meat on insulin resistivity and incidence of type 2 diabetes. The heating up of meat leads to the formation of AGEs (Advanced glycation end products) [10,11]. It is expected that the pro-inflammatory properties in AGEs may attribute towards the induced risk of type 2 diabetes [12]. Moreover, presence of saturated fatty acids in meat can even contribute to the risk of type 2 diabetes [13].

Cow's milk consumption and diabetes

Campbell's China Study 2005, a guide to nutrition and health reported that milk protein casein is not fit for human consumption. The proteins in cow's milk have been found to be responsible for auto-immune diseases especially type 1 diabetes; mostly in children with genetic susceptibility [14]. This was explained as, may be in most of us; the body's immune cells are unable to distinguish between the protein fragment of cow's milk and the β-cells of the body. Consequently, the immune cells attack the β-cells of the body resulting in diabetes or other autoimmune diseases [14].

An overview of medical literature on early cow's milk exposure and type 1 diabetes reported an increase of risk factors by approximately 1.5 times [15]. Higher anti-casein antibodies were also observed in children with type 1 diabetes [16]. In a popular study, a linear model was obtained on analyzing age-standardized prevalence of diabetes among children of 0-14 years of age in 12 countries. The countries were Finland, Sweden, Norway, Great Britain, Denmark, United States, New Zealand, Netherlands, Canada, France, Israel, and Japan [17] (Figure 2).

Among them, Finland had the highest incidence of insulin-dependent type 1 diabetes, which was 35 times higher than Japan. Finland has the world's highest cow's milk and milk products consumption and subsequently highest prevalence of diabetes [18]. The research concluded that cow's milk may be responsible for development of insulin-dependent type 1 diabetes.

Plant-based diet and diabetes

In support of plant-based diet, a cohort study involved 3,704 participants with 653 diabetes patients from European Prospective Investigation [19]. The study examined the association between intake of fruits, vegetables and fruits and vegetables in combination along

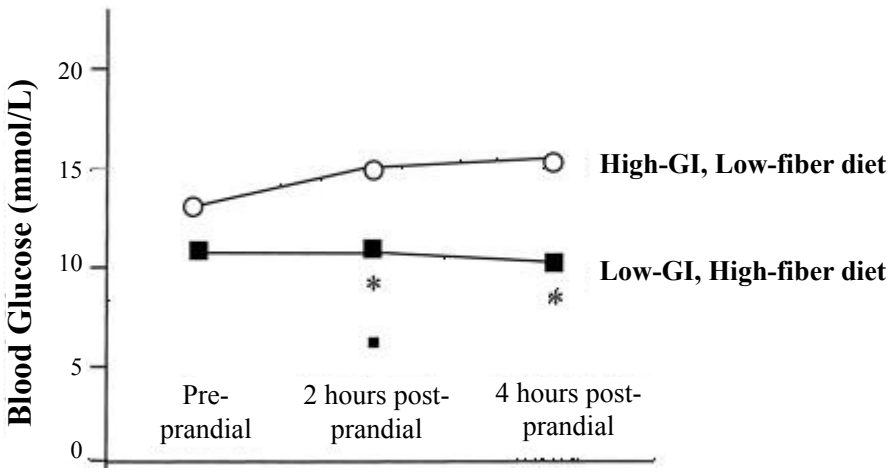

Figure 1: A 24 weeks analysis on post-prandial blood glucose concentrations obtained in type 1 diabetes patients with low GI-high fiber diet or high GI-low fiber diet (n=63).

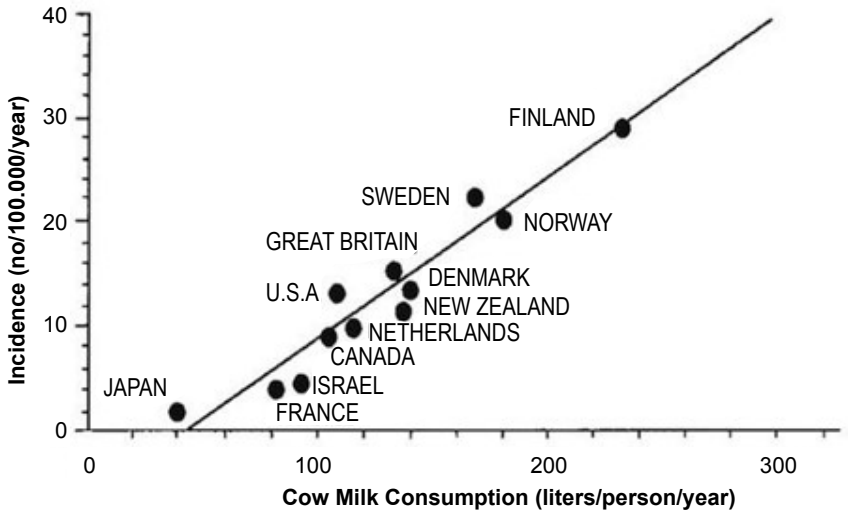

Figure 2: Association of Cow's milk Consumption and incidence of type 1 diabetes in different Countries.

with their variety and quantity and risk of type 2 diabetes [19]. The research analyzed 11-year incidence of type 2 diabetes, and reported 21% lower risk of diabetes with greater fruits and vegetables intake in diet (Cooper et al., 2012). A research based on epidemiological and clinical trials found that nuts can improve post-prandial glycemia and reduce the risk of diabetes [20]. Many studies have reported the relation between nut consumption and metabolic syndrome (MetS). Metabolic Syndrome is a group of cardio-metabolic risk factors, which comprise of type 2 diabetes, high fasting plasma glucose, hyperglycemia, hyper-triglycerides, low HDL cholesterol and abdominal obesity [21].

Metabolic syndrome raises the risk of diabetes by 5 times and that of cardiovascular diseases for diabetes population by 2 to 5 times [22]. Nuts have been found to play an important role in adjusting the components of MetS by influencing inflammation, oxidative stress, and endothelial function. This in process influences the insulin sensitivity and reduces chances of diabetes, hypertension and obesity [20].

Also, three cohort studies could establish a reduced risk of type 2 diabetes by 27%, 20% and 33% respectively by nut intake in regular diet in women in the Nurses' Health Study (NHS, in the NHS and NHS II cohorts) [23, 24] and women in the Shanghai Women's Health Study [25]. A significant research published in the Current Atherosclerosis Reports-2010 demonstrated that, the time of cooking is directly proportional to the increase in glycemic index (GI), resulting in lot of burden on the blood sugar making a person more prone to diabetes [26]. In the same research it was proved that the simple whole grain consumption in its natural state helps the diabetic patient to get a more stable and acceptable blood sugar. However, the refining followed by cooking of the grains rapidly shifts the grains from the low GI range to high GI range [26].

Research design

The 3-days Residential Treatment Tour was conducted at Zorba, The Buddha, 10-Tropical Drive, Ghitorni, New Delhi from 29th April to 1st May, 2016 with 55 diabetes patients and 6 Medical Analysts. The Residential Treatment Tour was publicized among masses both online and through seminars. The procedure required form-filling of DAM form-Diet and Medicine information by the patients. By the time of the beginning of the tour, 60 patients could furnish all details along with completion of the desired formalities of the tour. However, 5 of them had to leave because of personal reasons. Therefore, our sample-size was reduced to 55 patients. The procedure was planned to keep the 55 subjects on 3-days plant-based raw fruits and vegetables diet. The medicines were discontinued at the start of the plan. Meals were provided as per the diet plan with appropriate quantities based on the patient's weight. Regular blood-sugar readings - fasting and post-prandial were taken and individuals' log-sheets were further maintained. The diet plan was all different for 3-days and was especially designed to fulfill the nutritional requirements of the patients.

Table 1, gives the scheduler depicting the events for Day 1, Day 2 and Day 3. All the patients were provided the scheduler before the start of the reversal tour. The planner was followed strictly, and observations on blood glucose readings, fluctuations and related parameters were precisely documented (Table 1).

The ingredients that formed the plant-based diet have been listed in Table 2, along with the quantities per individual for 3-days of reversal tour (Table 2).

Establishment of blood glucose threshold

For the research trial, the diagnostic criteria for blood glucose levels in 55 diabetes patients was taken to be 250 mg/dl post-prandial sugar level. The study was structured taking two important variables as -

1.Controlled Blood Glucose Level*

2.Partially Controlled Blood Glucose Level*

Controlled Blood Glucose Levels: The controlled levels denoted the blood glucose range of ≤ 250 mg/dl without medicines and or insulin requirement, along with the prescribed diet in 3-days. In this group of people, the diet alone balanced the glucose levels, leading to zero requirement of medicine or insulin.

Partially Controlled Blood Glucose Levels: The partially controlled levels denoted the blood glucose range of ≤ 250 mg/dl with less than 50% of insulin intervention than prescribed earlier. In this group, the diet could help maintain the blood glucose readings with

DAY 1		DAY 2		DAY 3	
Time	Activity	Time	Activity	Time	Activity
7:20 AM	Reporting Time	7:20 AM	Reporting Time	7:20 AM	Reporting Time
7:30 AM	Blood Sugar Test	7:30 AM	Blood Sugar Test	7:30 AM	Blood Sugar Test
7:40 AM	Coconut water + Tulsi Leaves + ginger Take 15 minutes to sip it	7:40 AM	Coconut water + Tulsi Leaves + ginger Take 15 minutes to sip it	7:40 AM	Coconut water + Tulsi Leaves + ginger Take 15 minutes to sip it
8:00 AM	Pranayam and Light Exercise(optional)	8:00 AM	Pranayam and Light Exercise(optional)	8:00 AM	Pranayam and Light Exercise(optional)
8:30 AM	Breakfast	8:30 AM	Breakfast	8:30 AM	Breakfast
9:30 AM	Diabetes Management Training 1	9:30 AM	Diabetes Management Training 5	9:30 AM	Diabetes Management Training 8
11:30 AM	Sugar readings (Only insulin dependent patients)	11:30 AM	Sugar readings (Only insulin dependent patients)	10:30 AM	Sugar readings (Only insulin dependent patients)
11:45 AM		10:45 AM	Snacks + Tiffin Insulin Management Training	11:45 AM	Snacks + Tiffin
12:00	Question-Answers	12:00		12:00 noon	Diabetes Management Training (Maintenance Diet)
12:30 PM	Diabetes Management Training 2	12:30 PM	Diabetes Management Training 6	2:00 PM	Lunch
2:00 PM	Lunch	2:00 PM	Lunch	2:30 PM	Submit Log Sheet through mail
3:30 PM	Diabetes Management Training 3	3:30 PM	Queries	3:00 PM	Maintenance Diet through Whatsapp
5:00 PM	Blood Sugar (PP)	5:00 PM	Blood Sugar (PP)	3:30 PM	End of Tour
5:05 PM	Snacks + Tiffin	5:05 PM	Snacks + Tiffin		
5;15 pm	Question/Answers	5;15pm	Question/Answers		
5:30 PM	Question/Answers	5:30 PM	Question/Answers		
6:00 PM	Walk/free-time/dinnerpreparation	6:00 PM	Walk/free-time/dinner preparation		
7:00 PM	Dinner	7:00 PM	Dinner		
8:00 PM	Diabetes Management Training 4	8:00 PM	Diabetes Management Training 7		
9:45 PM	Blood Sugar Test	9:45 PM	Blood Sugar Test		

Table 1: Gives the day-wise scheduler followed during the reversal tour.

minimum and much reduced insulin dosage. For example, a 30 yrs male with 20U of insulin for the day, required only 3U of insulin under the diet therapy.

This cut-off limit has been well established in the book Last-Days of Diabetes [27]. Chowdhury (2016). For Doctors & Care Givers. The section 'Calculation' of the book brings out the core understanding of the world-wide establishment of blood glucose reference range as 250 mg/dl, Available at: https://www.biswaroop.com/9312286540.pdf

Findings of the study

The study reported 46 patients with controlled sugar levels and 9 with partially-controlled sugar levels. The valid percentages obtained were 84% and 16% under controlled and partially controlled groups respectively shown in Frequency Table and Correlation Table below (Table 3).

In this trial 21 patients were type 1 diabetic and 34 patients were type 2 diabetic. Among type 1 patients 57% could attain controlled blood glucose readings and 43% attainted partially controlled readings. Among type 2 diabetes patients, 100% gave controlled sugar readings through the process shown in correlation table below (Table 4).

The trial had 40% insulin-dependent cases, of these 59% could completely drop their insulin requirement to zero and 41% could reduce the levels by at least 50% of the earlier requirement shown in correlation table below (Table 5).

An important observation is that 100% results were obtained with patients with above 10 years of disease history, as all the 5 subjects maintained controlled sugar levels. For those newly diagnosed or less than 1 year of disease history, 78% could attain controlled blood glucose readings.

Below is Bar Chart-1 of two variables the attained sugar levels and disease duration in 55 Diabetes Patients (Figure 3).

Maximum number of patients were with a disease history of <1 year, 78% of these reported controlled readings, following them were patients within 1-5 years of disease history, who gave 92% controlled results, and 80% controlled results for the group with 5-10 years of disease history shown in frequency table below (Table 6).

The findings of the study gave 1.14 kilos of average weight loss per individual of total 55 cases. Among these, 9 subjects could reduce more than 3kilos of weight in 3-days of plant- based diet treatment along with good control over blood glucose levels. Almost half of the cases could reduce <1 kilos of weight during the trial.

Below is the pie-chart with valid-percentages of weight reduced among 55 subjects (Figure 4).

Of the total 55 subjects, 16% reduced ≥ 3 kilos of weight, following them were 20% of patients with 2-3 kgs of weight reduction and 14% could reduce 1-2 kilos of weight during 3-days. Whereas, 49% reported <1 kilo of weight reduction (Table 7).

Among patients with different age-groups, all of those ≥ 50 years of age could attain controlled sugar levels. Those below 20 years of age showed 40% controlled and 60% partially controlled sugar levels. This could be related to the little difficulty faced by young children to consume raw-food in those 3-days and report effective results. Below is the bar-chart plot between two variables-attained sugar levels and age groups in 55 diabetes patients (Figure 5).

The Bar Chart-2 clearly shows the maximum subjects ≥ 60 years of age under controlled group following them are the subjects in 30-40 age group, the 40-50 and 50-60 age groups had equally effective outcomes (Tables 8,9).

Results: Of 55 cases, 41 were males and 14 were females. Among them, 83% of males and 86% females could attain controlled blood glucose readings by the end of 3-days diet treatment. The outcomes clearly support the diet protocol to be equally effective in both the genders.

Green Drinking Coconut Water	5
Fresh Coconuts	3
Basil Leaves	100
Ginger(Adrak)	20 gm
Pomegranate	500 gm
Banana	8 in number
Papaya	500 gm
Oranges	500 gm
Apple	400 gm
Almonds	100 gm
Raisins	100 gm
Cashews	50 gm
Walnut	25 gm
Raw Sesame Seeds (White)	50 gm
Fig	6 (dried or fresh)
Raw Peanuts	300 gm
Dates	100 gm (without sugar coating)
Whole Moong Dal Sprouted	100 gm
Cucumber	1.5 kg
Tomato	1 kg
Beetroot	500 gm
Red or green Cauliflower	300 gm
French Beans (soft and tender)	250 gm
Onion	250 gm (optional)
Yellow/Red/ Green Pumpkin	400 gm
Bottle Gourd	250 gm
Red Bell Pepper	250 gm
Yellow Bell Pepper	250 gm
Capsicum	250 gm
Cabbage	250 gm
Spinach	1 kg
Green Chili	30 gm
Carrot	500 gm
Broccoli	250 gm
Mint Leaves	250 gm
Fresh Green Coriander	250 gm
Lemon	250 gm
Garlic	25 gm
Bay Leaves	6
Fresh and Tender Curry Leaves	400 gm
Fresh Beetle Leaves	1
Jaggery (Gur)	50 gm
Black Pepper Powder	10 gm
Cinnamon Powder	10 gm
Roasted Cumin Seeds	15 gm
Green Cardamom Powder	10 gm
Yellow Lentil	50 gm
Black Chick Peas	80gm
White Chick Grams	50 gm

Table 2: Gives the list of ingredients per participant for 3-days of reversal tour.

Sugar Levels					
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	**Controlled**	46	83.6	83.6	83.6
	Partially Controlled	9	16.4	16.4	100
	Total	55	100	100	
Frequency Table- 1					

Table 3: Controlled and Partially Controlled Blood Glucose Levels in 55 Diabetes Patients.

Sugar Levels * Diabetes Type Cross-tabulation				
Count		**Diabetes Type**		
		T ype 1	**Type 2**	**Total**
Sugar Levels	**Controlled**	12	34	46
	Partially Controlled	9	0	9
Total		21	34	55
Correlation Table-1				

Table 4: Sugar levels and Type 1 or 2 diabetes in 55 diabetes patients.

Sugar Levels * Insulin Dependency Cross-tabulation				
Count		**Insulin Dependency**		
		Insulin Dependency	**Insulin- Independent**	**Total**
Sugar Levels	**Controlled**	13	33	46
	Partially Controlled	9	0	9
Total		22	33	55
Correlation Table-2				

Table 5: Sugar levels and insulin dependency in 55 diabetes patients.

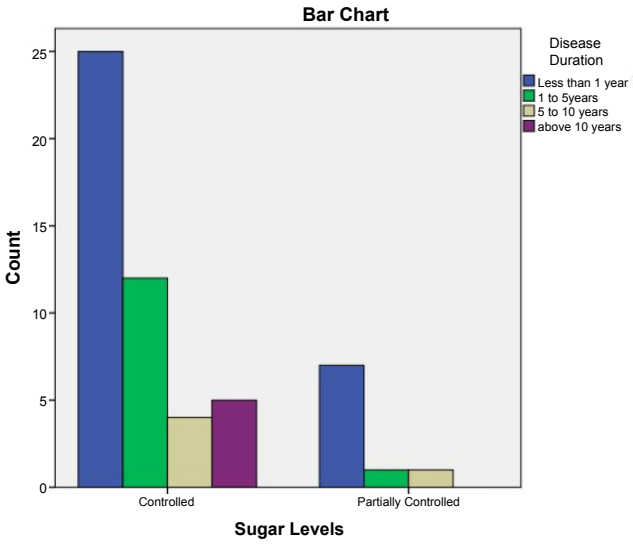

Figure 3: Bar Chart showing variables for the attained sugar levels and disease duration.

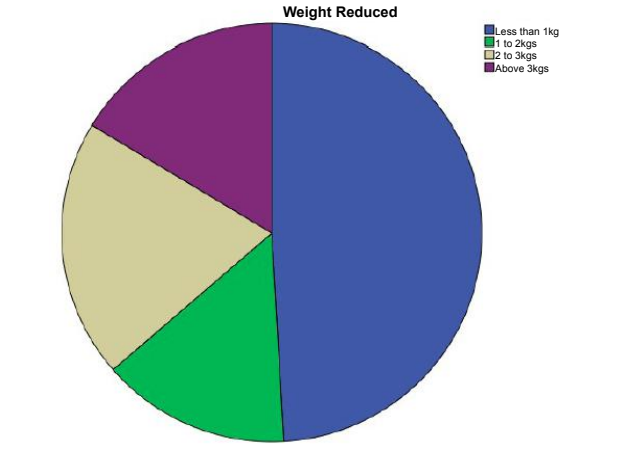

Figure 4: Pie-chart with valid-percentages of weight reduced among 55 subjects.

Sugar Levels * Disease Duration Cross-tabulation						
Count		Disease Duration				
		Less than 1 year	1 to 5 years	5 to 10 years	Above 10 years	Total
	Controlled	25	12	4	5	46
	Partially Controlled	7	1	1	0	9
Total		32	13	5	5	55
Correlation Table - 3						

Table 6: Sugar levels and disease duration in 55 diabetes patients.

Weight Reduction					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Less than 1kg	27	49.1	49.1	49.1
	1 to 2kgs	8	14.5	14.5	63.6
	2 to 3kgs	11	20	20	83.6
	Above 3kgs	9	16.4	16.4	100
	Total	55	100	100	
Frequency Table-2					

Table 7: Weight reduction in 55 diabetes patients.

Sugar Levels * Patient Age Cross-tabulation								
		Patient Age						
		Less than 20	20-30	30-40	40-50	50-60	Above 60	Total
Sugar Levels	Controlled	4	1	11	9	9	12	46
	Partially Controlled	6	1	1	1	0	0	9
Total		10	2	12	10	9	12	55
Correlation Table - 4								

Table 8: Sugar levels and age groups in 55 diabetes patients.

Sugar Levels * Patient Gender Cross-tabulation				
Count		Patient Gender		
		M ale	Female	Total
Sugar Levels	Controlled	34	12	46
	Partially Controlled	7	2	9
Total		41	14	55
Correlation Table - 5				

Table 9: Sugar levels and gender in 55 diabetes patients.

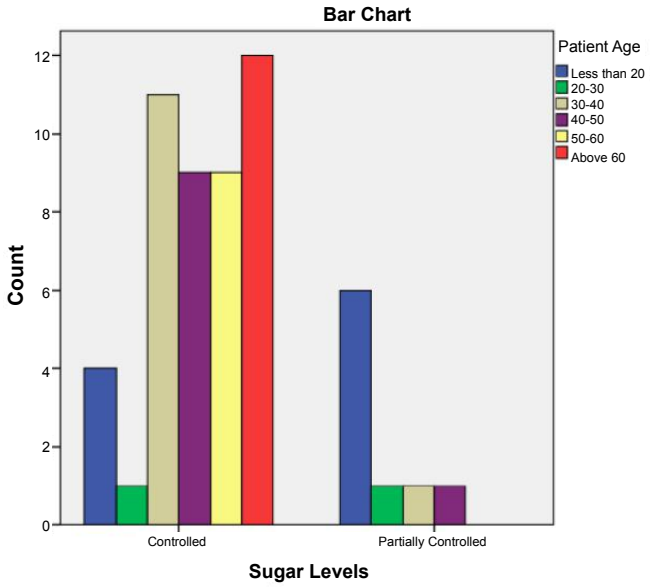

Figure 5: Bar chart showing the count and sugar level of the patients of different age group.

Conclusion

There had been extensive research on changes in life-style and diet to cure diabetes, but rare could establish a practical approach. Also, most research work is based on one particular type of food or parameter in terms of diabetes or cardiovascular diseases. Besides this, it is important to relate the nutritional fulfillment through diet in terms of healthy carbohydrates, proteins, fats, vitamins, minerals and anti-oxidants. Furthermore, consideration of body's metabolism through the functional and metabolic pathways can only provide the actual effect of the food in the body. The plant-based diet protocol has the similar design and works to aid the effective mechanisms in body. Eliminating the toxic components in food, the diet covers all the nutritional requirements.

The plant-based diet in the form of raw fruits and vegetables has the ability to reduce blood glucose levels both fasting and post-prandial. The diet is suitable for diabetic individuals. The diet has shown effect in case of both type 1 and type 2 diabetes patients. The diet process could reduce the insulin dependency for most of the patients by at least 50%. Disease duration was not a hindrance, as similar effects were seen in subjects with above 10 years of disease history and with newly diagnosed diabetes patients. The diet proved to be beneficial irrespective of variable age groups and demographic profiles. Besides, weight reduction by plant-based diet with quality nutrition makes the diet suitable for diseases associated with obesity or high fatty acids and related metabolic and cardiovascular diseases.

Post tour follow-ups

The necessary follow-ups were practiced post 3-days of Residential Tour. Most of the patients who maintained the diet protocol in their routine gave affirmative response. For most of them their medications completely dropped. Few of them could even maintain a healthy life-style with no-medicines even for common fevers. The remaining, who were still on medicines have been reducing them slowly with the diet-protocol. Follow-ups and advices are still carried over when required.

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SIMPLE STEPS TO REVERSE DIABETES IN 72 HOURS

As you have seen in my research paper (section IV), that 80% of my patients were off medication/insulin within 72hrs during my "72 Hours Diabetes Tour". You too can achieve the same, just follow the procedure given as under :-

Phase I : In next 24 hrs to 48 hrs try to adjust the medication/insulin. Here, refer to Guideline statement 3 (section I/II), i.e. if your blood sugar goes below 170mg/dl or 9.4mmol/lt while on medication, then you need to taper down the drug/insulin so as to keep the blood sugar more than 170mg/dl or 9.4mmol/lt and preferably less than 244mg/dl or 13.5mmol/lt (as in guidance statement -2).

Phase II : Now, the final goal is to keep the blood sugar below 244mg/dl without the medication/insulin. For that follow DIP Diet (for more details about DIP Diet refer to the book "Diabetes Free World"):-

Steps to design your DIP Diet

Step I:- Till 12 noon, eat only fruits of 3 to 4 types including mango, banana, grapes, etc.

*Minimum amount to be consumed = Your body weight in kg × 10 = ……..gms

For example, a 70kgs person should consume atleast 700gms of 4 types of fruits before 12 noon.

Step II:- Always eat your lunch/dinner in 2 plates. Plate 1 and Plate 2

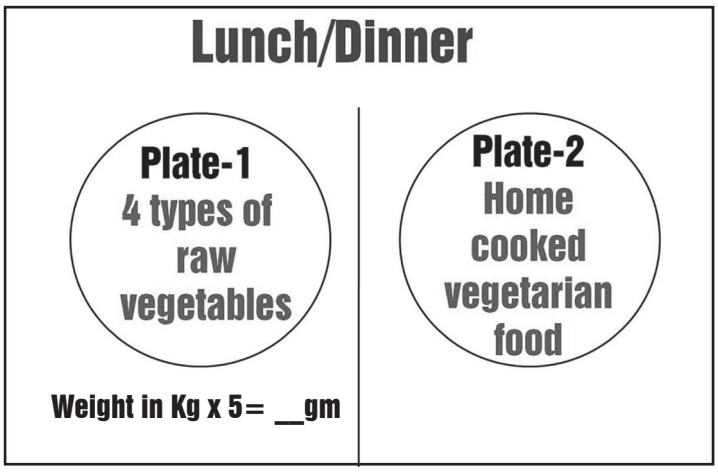

Plate 1 should consist of 4 types of vegetables like carrot, tomato, radish and cucumber, which you can eat in raw form.

*Minimum amount in Plate 1 = Your body weight in kg × 5 = …….. gms

For example, a 70 kg person should eat at least 350gms of 4 types of raw vegetables.

Plate 2 consists of home cooked vegetarian food with negligible salt and oil.

First finish eating plate 1, in accordance with the above calculation. Then take plate 2 as much as you want to eat. The rules for lunch and dinner are same; however, we must remember to try to finish dinner by 7pm.

Step III:- AVOID

1. Animal food including milk products
2. Multivitamin tonic and capsules
3. Refined and packed food

*Try exposing your body to 40 minutes of sunshine on daily basis.

Other than 3 main meals of breakfast, lunch and dinner – following are the options for snacks/beverages:-

1. Sprouts (Body weight in Kg = ……..gms)

Example: For 70kg person about 70gms of sprouts in a day.

2. All kinds of 'Nuts' can be consumed after soaking in water for 2-3 hours. Quantity = Body weight in kg = …….gms

Example: For 70kgs person about 70gms of nuts in a day.

3. Fruits can also be consumed as snacks.

4. Fresh coconut water and coconut cream.

5. Hunza tea (see recipe on front inner of the book)

The above diet will help you to drastically lower the blood sugar within the 1st 72hrs of following the diet. So, keep tapering the medication/insulin as discussed in phase I.

On the basis of my experience with more than 20,000 patients in last 10 years, I can say that, about 70% to 80% of the diabetes patients will not only be off medicine within 72hrs of following the above diet, but also within first 10 days, their blood pressure will start to normalize (among those who were on hypertensive drugs), getting rid of B.P. medicines as well.

Kindly note, even after being free of medicines the above diet should become a permanent part of your life-style with the exception of occasional cheating especially when you go on an outing or a marriage party etc. You can deviate from the above rules not more than once in ten days. That is the only sure shot way to remain healthy and prevent future occurrence of diabetes or hypertensive condition or even heart disease.

About 20% to 30% of the patients may still need a part of medication/insulin in spite of following the above diet. This is a clear indication that their pancreas are critically damaged. They need little amount of patience to keep following my recommended diet for nearly 1 month to 3 months to get free from medication or may get benefitted from the Advance Diet.

To know about the advance diet you may read my book “Diabetes Free World” or go to my You-tube channel – Dr. Biswaroop Roy Chowdhury and watch my video “The 4th Gear Diet.”

At the end I would like to conclude –

“No one needs to die or live with Diabetes”

It's your chance to reverse Diabetes

Join

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Be under the direct supervision of
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Diagnosis, Drugs and Diabetes
.....Forever

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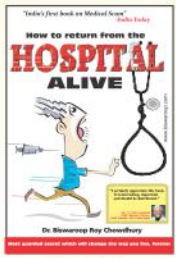

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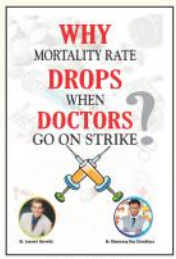

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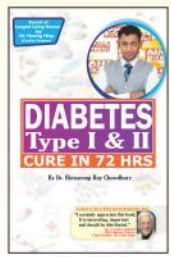

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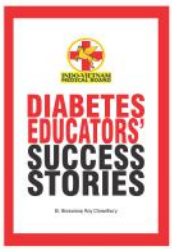

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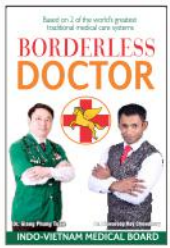

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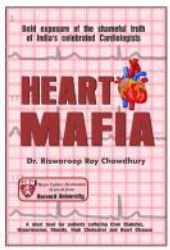

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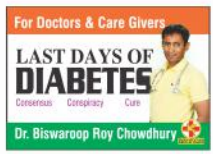

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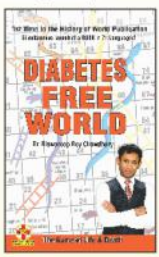

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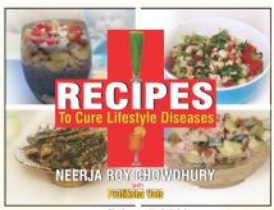

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New Research : A Hope for a Diabetes Free World

From page 6...

It's a sigh of relief that the mainstream medical science has corrected the protocol for Diabetes patients, but sadly the modern doctors decided not to pass on this extremely important and beneficial knowledge to their diabetic patients as it may mean contradicting their own preachings and recommendations which they were practicing for many decades.

Dr. Biswaroop Roy Chowdhury

- Ph. D in Diabetes Reversal "Alliance International University" Zambia
- Post Graduation in Diabetes Education- IDF
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