Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus

Brandy A. Urbanowicz
Pacific University

Recommended Citation
Urbanowicz, Brandy A., "Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus" (2015). School of Physician Assistant Studies. 523. https://commons.pacificu.edu/pa/523

This Capstone Project is brought to you for free and open access by the College of Health Professions at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.
Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus

Abstract

Background: Type 2 diabetes mellitus is a chronic disease that has been increasing in prevalence in the United States every year. Diabetes is associated with numerous physical health complications, most notably the development of cardiovascular disease. In addition, the financial burden imposed by diabetes is great and includes medical costs and lost work time. Most patients with diabetes take prescription oral anti-diabetic medications (OADs) but still do not have adequate glycemic control. When adequate glycemic control is not achieved with these medications, injectable insulin is then required; it is understandable that patients object to this type of invasive treatment and would prefer to remain on oral therapies. Over-the-counter dietary supplements, specifically chromium picolinate and biotin, have been studied for their efficacy as glycemic control agents; the purpose of this metasynthesis was to review existing literature pertaining to concurrent use of both chromium picolinate and biotin supplements as adjunct therapy to prescription OADs to determine if improved glycemic control is achieved in patients with type 2 diabetes mellitus.

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: diabetes, chromium picolinate and biotin. Relevant articles were assessed for quality using the GRADE system. A search on the NIH clinical trials site revealed there are no trials currently registered relating to the concomitant use of chromium picolinate and biotin in patients with type 2 diabetes mellitus.

Results: Ninety-six articles were reviewed for relevancy; two met inclusion criteria and were included in this systematic review. Both studies included were randomized, double blind, placebo-controlled trials that found a statistically significant improvement in glycemic control with dual chromium picolinate and biotin treatment.

Conclusion: Chromium picolinate and biotin appear to modestly improve glycemic control. Chromium picolinate and biotin are safe, over-the-counter supplements; due to evidence obtained from prior animal studies, the lack of significant adverse drug reactions and modest-to-substantial blood-glucose reducing effects, chromium picolinate and biotin supplementation as adjunct therapy to prescription OADs may be clinically justified.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Annjanette Sommers, PA-C, MS

Keywords
Type 2 diabetes mellitus, chromium picolinate, biotin, glycemic control, human

Subject Categories
Medicine and Health Sciences

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/523
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus

Brandy A. Urbanowicz

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, Oregon
For the Masters of Science Degree, August 8, 2015

Faculty Advisor: Duc Vo, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Brandy A. Urbanowicz hails from the mountain town of Gunnison, Colorado. She received a Bachelor of Arts degree from Western State Colorado University in 2012 and majored in Biology with an emphasis on Cell Biology/Pre-Medicine. Prior to PA school she had experience as a volunteer EMT-B and worked as a CNA. After PA school she plans to work in Primary Care in rural communities, in both the United States and abroad.
Abstract

**Background:** Type 2 diabetes mellitus is a chronic disease that has been increasing in prevalence in the United States every year. Diabetes is associated with numerous physical health complications, most notably the development of cardiovascular disease. In addition, the financial burden imposed by diabetes is great and includes medical costs and lost work time. Most patients with diabetes take prescription oral anti-diabetic medications (OADs) but still do not have adequate glycemic control. When adequate glycemic control is not achieved with these medications, injectable insulin is then required; it is understandable that patients object to this type of invasive treatment and would prefer to remain on oral therapies. Over-the-counter dietary supplements, specifically chromium picolinate and biotin, have been studied for their efficacy as glycemic control agents; the purpose of this metasynthesis was to review existing literature pertaining to concurrent use of both chromium picolinate and biotin supplements as adjunct therapy to prescription OADs to determine if improved glycemic control is achieved in patients with type 2 diabetes mellitus.

**Methods:** An exhaustive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: diabetes, chromium picolinate and biotin. Relevant articles were assessed for quality using the GRADE system. A search on the NIH clinical trials site revealed there are no trials currently registered relating to the concomitant use of chromium picolinate and biotin in patients with type 2 diabetes mellitus.

**Results:** Ninety-six articles were reviewed for relevancy; two met inclusion criteria and were included in this systematic review. Both studies included were randomized, double blind, placebo-controlled trials that found a statistically significant improvement in glycemic control with dual chromium picolinate and biotin treatment.

**Conclusion:** Chromium picolinate and biotin appear to modestly improve glycemic control. Chromium picolinate and biotin are safe, over-the-counter supplements; due to evidence obtained from prior animal studies, the lack of significant adverse drug reactions and modest-to-substantial blood-glucose reducing effects, chromium picolinate and biotin supplementation as adjunct therapy to prescription OADs may be clinically justified.

**Keywords:** Type 2 diabetes mellitus, chromium picolinate, biotin, glycemic control, human
Acknowledgements

Special appreciation is given to Professor Annjanette Sommers, for the extra effort she gave to help me put this project together;

And to my dear Forest Ocean, without whom I never would have gone to college, and whose love, support and never-ending belief in me made this all possible.
# Table of Contents

- Biography ........................................................................................................... 2
- Abstract ................................................................................................................ 3
- Acknowledgements .............................................................................................. 4
- Table of Contents ............................................................................................... 5
- List of Tables ........................................................................................................ 6
- List of Abbreviations ........................................................................................... 6
- Background ......................................................................................................... 7
- Methods ............................................................................................................... 9
- Results ............................................................................................................... 9
- Discussion ......................................................................................................... 14
- Conclusion ....................................................................................................... 17
- References ....................................................................................................... 18
- Tables .............................................................................................................. 24
List of Tables

Table 1: GRADE Quality of Assessment
Table 2: Summary of Findings

List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reactions</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>ApoA</td>
<td>Apolipoprotein A</td>
</tr>
<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>AUCg</td>
<td>Area Under Curve, glucose</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>CrPic</td>
<td>Chromium Picolinate</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebrovascular Accident</td>
</tr>
<tr>
<td>DKA</td>
<td>Diabetic Ketoacidosis</td>
</tr>
<tr>
<td>DMT2</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluations</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated Hemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institute of Health</td>
</tr>
<tr>
<td>OAD</td>
<td>Oral Anti-Diabetic Medication</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the Counter (non-prescription)</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very Low Density Lipoprotein</td>
</tr>
</tbody>
</table>
Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus

BACKGROUND

The prevalence of diabetes, especially type 2 diabetes mellitus (DMT2) in the United States has been increasing every year.\textsuperscript{1} As of 2011, 8.5\%, or almost 20 million of U.S. adults have physician-diagnosed diabetes, with another estimated 11 million adults with undiagnosed diabetes. Of this combined approximate 31 million, 90\%-95\% have DMT2.\textsuperscript{2,3}

The physical complications of diabetes are vast and include, but are not limited to, significant cardiac, hepatic, and renal diseases.\textsuperscript{4-11} In addition to the physical health complications, diabetes takes a substantial economic toll. In 2012, total economic burden of diabetes including medical costs, disability, work loss and premature death was estimated at $245 billion.\textsuperscript{12} The costs of health complications alone attributable to diabetes is on average $47,240 per patient over 30 years.\textsuperscript{13}

Both health and financial consequences can be reduced if patients with diabetes obtain adequate glycemic control. Glycemic control can be obtained through weight loss and careful attention to diet for many,\textsuperscript{14} but the majority of overweight or obese people are either unsuccessful complying with a weight loss regimen or are unsuccessful at maintaining any weight lost.\textsuperscript{15,16} As a result, most patients with DMT2 take prescription oral anti-diabetic medications (OADs). Approximately 85.6\% of patients with diabetes take OADs, insulin, or both.\textsuperscript{12} The most frequently used medications reduce glycated hemoglobin (HbA1c) on
average between 1%-2% and are metformin, sulfonylureas, and thiazolidinediones, but they come with numerous adverse drug reactions (ADRs) including diarrhea, lactic acidosis, weight gain, hypoglycemic events, hepatotoxicity, and congestive heart failure.\textsuperscript{17-20}

Chromium deficiency has been shown to cause insulin resistance and diabetes,\textsuperscript{21} so it has been postulated that chromium supplementation can reverse these conditions.\textsuperscript{22,23} Chromium supplementation has been studied as a blood-glucose lowering agent in both animal and human models with mixed results.\textsuperscript{23,24} One study\textsuperscript{23} found supplemental chromium had little effect lowering blood glucose on the entire study cohort as a whole, but found a significant lowering of HbA1c and increased insulin sensitivity compared to baseline in a cohort subset considered “responders”. Another study\textsuperscript{25} demonstrated a decreased requirement for exogenous insulin with chromium administration.

In addition to chromium, biotin treatment has been shown to improve insulin resistance and impaired glucose tolerance as well as decrease blood glucose in several animal studies.\textsuperscript{26-30} In one study,\textsuperscript{27} genetically diabetic mice were given various levels of biotin; after 10 weeks the mice demonstrated lowered post-prandial glucose levels and improved insulin resistance. In three other studies involving diabetic rats, biotin was shown to prevent insulin resistance in skeletal muscle\textsuperscript{28} and to improve impaired glucose tolerance.\textsuperscript{29,30} More importantly, in a human study, poorly-controlled diabetics showed a significantly improved fasting glucose after receiving biotin for one month.\textsuperscript{31} Results of these studies have lead researchers to consider dual treatment with chromium and biotin as adjunct therapy to prescription OADs for glycemic control improvement in patients with DMT2.
METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: diabetes, chromium picolinate and biotin. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating the effectiveness of dual therapy with CrPic and biotin for glycemic control improvement in people with DMT2 were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.\(^{32}\) A search on the NIH clinical trials site revealed no currently registered trials relating to the use of CrPic combined with biotin in patients with DMT2.

RESULTS

The initial result of the search yielded 98 articles for review; 8 from Medline-OVID, 64 from CINAHL and 26 from Web of Science. After screening relevant articles for randomized controlled trials, adult patients with DMT2, human subjects and English language studies, a total of two articles met inclusion criteria.\(^{33,34}\) Refer to Tables 1 and 2 for the GRADE evaluation and summary of results.

Singer et al study

This is a randomized, double blind, placebo-controlled trial\(^{33}\) which looked at the effect of oral CrPic and biotin at improving glycemic control in overweight patients with uncontrolled, treated DMT2.\(^{33}\)

Glycemic control was measured via plasma fructosamine, insulin and fasting glucose levels, area under curve for glucose (AUCg) and oral glucose tolerance test (OGTT)
measured at 30, 60, 90 and 120 minutes. Secondary endpoints were effects on total cholesterol as well as the cholesterol fractions HDL, LDL, VLDL, ApoA, and ApoB, triglycerides and triglyceride:HDL ratio. The trial enrolled 43 subjects at a single study site in the United States.  

Eligibility criteria consisted of patients who were overweight or obese classified with a body mass index (BMI) \( \geq 25 \) to \( \leq 35 \) kg/m\(^2\); between the ages of 18 and 65; a diagnosis of DMT2 for \( \geq 1 \) year; poorly-controlled (HbA1c \( \geq 7.0\%)\); persistent impaired glucose control (2-h glucose >200 mg/dL); and stable on OADs prior to study entry. OADs allowed were metformin, sulfonylureas, and thiazolidinediones, but the amount and duration of OADs were not controlled for in the study. Exclusion criteria consisted of patients who were currently on or required insulin treatment. 

Subjects were assigned 1:1 to either a treatment group in which they received 600 µg Cr\(^{3+}\) in the form of CrPic and 2 mg biotin, or a placebo group, with a study length of 30 days. CrPic and biotin were administered as a single capsule manufactured under the name Diachrome® by Nutrition 21, Inc., Purchase, NY. Although the study states it was a randomized, double-blind trial it does not give details pertaining to how randomization or blinding occurred. 

Both the treatment group and placebo group were balanced at the beginning of the study with respect to demographics, ie, age, sex, race, weight, height, BMI and blood pressure (BP), as well as baseline HbA1c (p= 0.1430 to 0.9787). Of the 43 randomized patients at the study beginning, seven (16.3%) were either lost to follow-up or excluded for protocol violations; one patient was lost from the treatment group and six lost from the placebo group. Data were collected on 36 patients considered eligible for analysis after these
losses; 20 patients were assigned to the treatment group and 16 patients were assigned to the placebo group.\textsuperscript{33}

Data were recorded as mean values ± SD (see Table 2). Treatment with CrPic and biotin significantly \textit{reduced} fructosamine by 23.0 ± 56 mg/dL (p= 0.3698), as compared to placebo which \textit{increased} by 12.9 ± 33 mg/dL (p= 0.5980); the comparison of the mean changes between treatment and placebo was p= 0.0263. Fasting glucose in the treatment group increased by 7.45 ± 65 mg/dL (p= 0.6597) as compared to placebo which increased by 50.19 ± 62 mg/dL (p= 0.0580); treatment vs. placebo was p= 0.0525. Insulin resulted in no significant change in either the treatment or placebo groups. AUCg \textit{reduced} in the treatment group by 4701.8 ± 8959 min • mg/dL (p= 0.0441) but \textit{increased} in the placebo group by 1649 ± 7013 min • mg/dL (p= 0.5702); treatment vs. placebo was p= 0.0264. OGTT at 30, 60, 90 and 120 minute intervals all decreased in the treatment group but the changes were not considered statistically significant according to p-values.\textsuperscript{33}

Based on the statistical significance of decrease in fructosamine and AUCg levels vs. placebo and the lack of hypoglycemic events or serious ADRs in this study, the authors of this study recommended the use of CrPic and biotin supplements to enhance glycemic control.\textsuperscript{33}

\textit{Albarracin et al study}

This randomized, double blind, placebo-controlled trial\textsuperscript{34} examined the effect of oral CrPic and biotin at improving glycemic control in overweight patients with uncontrolled, treated DMT2. Glycemic control was measured via serum HbA1c and fasting insulin and glucose levels. Secondary endpoints were effects on total cholesterol as well as the
cholesterol fractions HDL, LDL, and VLDL, triglycerides, and triglyceride:HDL ratio. The trial enrolled 447 subjects from 17 sites in the United States.\textsuperscript{34}

Eligibility criteria consisted of patients who were overweight or obese (BMI ≥25 to <35 kg/m\(^2\)); between the ages of 18 and 70; a diagnosis of DMT2 according to ADA criteria for ≥1 year; poorly-controlled (HbA1c ≥7.0%); stable on OADs for ≥60 days prior to study entry; and fasting triglyceride level ≤400 mg/dL. Type, amount, and duration of OADs were not controlled for in the study. Exclusion criteria was extensive and consisted of the following: diagnosis of type 1 diabetes mellitus; hypoglycemic events requiring emergency transport ≤12 months; supplementation with CrPic within 90 days and/or any other form of chromium ≥120 µg/d within 30 days; daily insulin usage or rescue insulin usage >1 time per week; an incidence of DKA ≤12 months; creatinine, AST or ALT ≥2.0 x ULN; total bilirubin ≥1.5 x ULN; cardiovascular conditions requiring hospitalization ≤12 months; history of CVA, PE or unresolved DVT; uncontrolled high BP ≥160 mmHg systolic or ≥90 mmHg diastolic (seated); serious immunosuppressive disorder or current immunosuppressive therapy; disorders of the liver, thyroid, or kidneys or other disorders known to affect glucose or lipid metabolism; alcoholism or substance abuse; mental health issues that would prevent the subjects from completing the study; and women who were pregnant or nursing.\textsuperscript{34}

Subjects were assigned 2:1 to either a treatment group in which they received 600 µg Cr\(^{3+}\) in the form of CrPic and 2 mg biotin, or a placebo group, with a study length of 90 days. As in the Singer et al\textsuperscript{33} study, CrPic and biotin were administered as a single capsule manufactured under the name Diachrome® by Nutrition 21, Inc., Purchase, NY. Randomization occurred via standardized computer software. The study medication was randomized by personnel unaffiliated with the study from Nutrition 21, Inc., who kept
records of the randomization schedule and blinding codes. All study site personnel were
blinded to which subjects received treatment.34

Both the treatment group and placebo group were balanced at study commencement
with respect to demographics, ie, age, sex, race, weight, height, BMI and BP (p= 0.06 to
0.53). Of the 447 randomized patients at the study beginning, 78 (17.4%) were dropped or
lost to follow-up, and an additional 21 had significant protocol violations not originally
accounted for. Numerical differentiation data for loss to follow-up between the treatment and
placebo groups were not presented; however, the authors stated there was no significant
difference in attrition rates between the treatment and placebo groups.34

Data were collected on 348 patients considered eligible for analysis after these losses;
226 patients were assigned to the treatment group and 122 patients were assigned to the
placebo group. Data were recorded as mean values ± SEM (see Table 2). Treatment with
CrPic and biotin significantly reduced HbA1c by 0.54 ± 0.15% (p= 0.0001), as compared to
placebo reduction of 0.34 ± 0.15% (p= 0.0001); treatment vs. placebo was p= 0.03. In a
subset of study patients whose initial HbA1c was >10.0%, a much greater reduction of 1.76 ±
0.23% (p= 0.0001) was seen; placebo reduction in this group was 0.68 ± 0.30% (p= 0.006),
and treatment vs. placebo in this group was p= 0.005. Fasting glucose overall was reduced by
9.8 ± 8.5 mg/dL (p= 0.002) as compared to placebo which actually increased by 0.7 ± 5.9
mg/dL (p= 0.84); treatment vs. placebo was p= 0.02. Fasting insulin resulted in no
statistically significant change in either the treatment or placebo groups. Based on the
statistical significance of these results and the lack of hypoglycemic events or serious ADRs,
the authors of this study made recommendations for the use of CrPic and biotin supplements
to further lower HbA1c.34
DISCUSSION

The goal of this systematic review was to explore the possibility that two OTC dietary supplements, CrPic and biotin, may further improve glycemic control in patients with DMT2 as adjunct therapy to prescription OADs. Two studies were found\textsuperscript{33,34} that provide some evidence that these supplements may be effective.

A single combination supplement, Diachrome®, was tested in both the Singer et al\textsuperscript{33} and Albarracin et al\textsuperscript{34} studies. As of this writing, Diachrome® was no longer offered by Nutrition 21, Inc., and attempts to contact Nutrition 21, Inc. for more information on this supplement were unsuccessful. Although a 2012 study found that CrPic and biotin supplementation decreased serum glucose and in a diabetic rat model,\textsuperscript{35} no human studies were found that tested both CrPic and biotin as separate supplements.

The patients in the Singer et al\textsuperscript{33} and Albarracin et al\textsuperscript{34} studies examined in this review, in which the supplement Diachrome® was used, did not experience serious ADRs or hypoglycemic events. This is in stark contrast to the numerous ADRs patients experience with the use of standard prescription OADs. For example, first-line prescription OAD treatment for a newly-diagnosed patient with DMT2 is either metformin or a sulfonylurea.\textsuperscript{36} Between 20-30% of patients experience unpleasant gastrointestinal effects including nausea, vomiting, diarrhea and excess flatulence while using metformin.\textsuperscript{18,37,38}

Prescription OADs offer an average of 1-2% reduction in HbA1c.\textsuperscript{42,43} The Albarracin et al\textsuperscript{34} study demonstrated modest overall HbA1c reduction of 0.54% and a substantial HbA1c reduction of 1.76% in those with baseline HbA1c >10.0%; these reductions are similar to those seen with prescription OADs. In both the Singer et al\textsuperscript{33} and Albarracin et al\textsuperscript{34} studies, ADRs that occurred with therapeutic doses of CrPic and biotin were not significant.
and were not different from placebo. The lack of significant ADRs seen with CrPic and biotin use in both studies are promising results. Moreover, the FDA considers both CrPic and biotin to be generally recognized as safe (GRAS) dietary supplements, even at doses significantly higher than what were used in these studies.\textsuperscript{44}

Although not specifically examined in this paper, it is interesting to note that the triglyceride:HDL ratio significantly reduced in the treatment groups in both the Singer et al\textsuperscript{33} study (treatment vs. placebo $p = 0.0453$) and the Albarracin et al\textsuperscript{34} study (treatment vs. placebo $p = 0.05$). Also, a statistically significant triglyceride level decrease was observed in the treatment group in the Singer et al\textsuperscript{33} study (treatment vs. placebo $p = 0.0159$). Changes in the other lipid values measured in both studies were not statistically significant from placebo.

Risk for potential bias was seen in both studies. Publication bias is a possible factor in both the Singer et al\textsuperscript{33} and Albarracin et al\textsuperscript{34} studies, due to the fact that funding was provided for both studies by Nutrition 21, Inc., maker of Diachrome®, the therapy in question. Referral bias may have occurred in the Singer et al\textsuperscript{33} study since it was conducted at a single site and gave no details pertaining to how patient selection or recruitment occurred. Selection bias did not appear to play a significant role in either of the studies; the patient demographic data were not found to be dissimilar between the treatment and placebo groups. Attrition bias is in question for the Singer et al\textsuperscript{33} study due to the fact that six out of the seven lost to follow-up were from the placebo group.

One important flaw concerning both studies was that neither controlled for amount or type of prescription OADs patients were taking at the beginning of the study. Prescription OADs were not considered statistically significant between treatment and placebo groups in
the Albarracin et al\textsuperscript{34} study (p= 0.85); the Singer et al\textsuperscript{33} study did not present these values. It is unknown if concomitant usage of OADs had an impact on the data, whether increasing or decreasing glycemic control effects obtained from CrPic and biotin use. Another important flaw in both studies was the small patient sample size, having been n= 43 and n= 447 in the Singer et al\textsuperscript{33} and Albarracin et al\textsuperscript{34} studies, respectively. These patient sample sizes may not be adequate for the results to relevantly apply to the vast diabetic population as a whole.

The duration of the Albarracin et al\textsuperscript{34} study (90 days) was sufficient enough to obtain post-treatment HbA1c results. Although the OGTT was considered the gold standard for measurement of glycemic control, it has largely been replaced clinically by HbA1c; HbA1c gives the value of blood-glucose levels over the prior 2-3 months.\textsuperscript{45-47} HbA1c was not used in the Singer et al\textsuperscript{33} study because the study duration was 30 days; as a consequence, plasma fructosamine was used post-treatment for data collection due to the fact that it will provide a blood-glucose value for the prior 2-3 weeks.\textsuperscript{48} Similar to HbA1c, fructosamine gives a reasonable estimation of blood glucose, though fructosamine measures glycated serum proteins, as opposed to HbA1c which measures glycated serum hemoglobin. Fructosamine measurement does not provide an exact correlation to HbA1c, but it can be used as a rough surrogate marker for HbA1c.\textsuperscript{45,46,49}

Unfortunately the studies did not use the same patient inclusion and exclusion criteria. Inclusion criteria was very similar between studies; however, while the exclusion criteria was limited in the Singer et al\textsuperscript{33} study, it was extensive in the Albarracin et al\textsuperscript{34} study. This may be overlooked considering the Singer et al\textsuperscript{33} study was the first study of its kind in humans, and was deemed a “pilot” study by the authors. It was apparent that the Albarracin et al\textsuperscript{34} study was designed to further investigate the effects of CrPic and biotin based on the
results of the Singer et al\textsuperscript{33} study. Both studies show promise, but again are limited because of their origination and small patient sample sizes.

CONCLUSION

The vast majority of the 20 million diagnosed diabetic adults in the U.S. have DMT2, which is associated with numerous physical health complications and a substantial economic burden. In addition to lifestyle changes, prescription OADs are beneficial in order to improve glycemic control, but for many the existing OADs are not sufficient. The combination of CrPic and biotin appear to have a modest impact on glycemic control improvement, but may have a larger benefit for those with an HbA1c of >10.0\%. Based on the GRADE criteria used to evaluate the studies reviewed, the overall combined quality is low, and only a weak recommendation can be made for adjunct therapy of CrPic and biotin supplementation to improve glycemic control. However, considering the safety of CrPic and biotin, the evidence obtained from prior animal studies, the lack of significant ADRs and modest-to-substantial blood-glucose reducing effects seen in the two studies reviewed herein, it appears that CrPic and biotin supplementation as adjunct therapy to prescription OADs can be clinically justified. These results are promising, and warrant further investigation via additional randomized controlled studies using larger patient sample sizes, into the use of these seemingly benign and to some extent effective DMT2 therapies.


TABLE 1. Characteristics of Reviewed Studies, GRADE profile

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td><strong>Fructosamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer et al[33]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious imprecision (^a)</td>
</tr>
<tr>
<td><strong>AUC glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer et al[33]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious imprecision (^a)</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer et al[33]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious imprecision (^a)</td>
</tr>
<tr>
<td>Albarracin et al[34]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
</tr>
<tr>
<td><strong>Fasting Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer et al[33]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious imprecision (^a)</td>
</tr>
<tr>
<td>Albarracin et al[34]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albarracin et al[34]</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
</tr>
</tbody>
</table>

\(^a\)Singer et al[33] study had a small sample size (n= 36); short study length of 30 days therefore HbA1c could not be measured

\(^b\)Singer et al[33] study, Albarracin et al[34] study; funded by the manufacturer of the chromium picolinate/biotin supplement that was tested

\(^c\)Albarracin et al[34] study graded low for HbA1c due to the fact that it was the only study that measured this outcome
## Summary of Findings

<table>
<thead>
<tr>
<th>Glycemic Control Marker</th>
<th>Study</th>
<th>Number of Patients</th>
<th>Effect</th>
<th>p-value</th>
<th>p-value vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment (total)</td>
<td>Placebo or no treatment (total)</td>
<td>Improvement compared to baseline</td>
<td></td>
</tr>
<tr>
<td>Fructosamine</td>
<td>Singer et al\textsuperscript{23}</td>
<td>20</td>
<td>16</td>
<td>-23.0 mg/dL</td>
<td>0.0263</td>
</tr>
<tr>
<td></td>
<td>Albarracin et al\textsuperscript{24}</td>
<td>226</td>
<td>122</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>AUC glucose</td>
<td>Singer et al\textsuperscript{23}</td>
<td>20</td>
<td>16</td>
<td>-6701.8 min × mg/dL</td>
<td>0.0441</td>
</tr>
<tr>
<td></td>
<td>Albarracin et al\textsuperscript{24}</td>
<td>226</td>
<td>122</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>Singer et al\textsuperscript{23}</td>
<td>20</td>
<td>16</td>
<td>+7.45 mg/dL</td>
<td>0.6597</td>
</tr>
<tr>
<td></td>
<td>Albarracin et al\textsuperscript{24}</td>
<td>226</td>
<td>122</td>
<td>-9.8 mg/dL</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>Singer et al\textsuperscript{23}</td>
<td>20</td>
<td>16</td>
<td>+0.005 µ U/mL</td>
<td>0.9957</td>
</tr>
<tr>
<td></td>
<td>Albarracin et al\textsuperscript{24}</td>
<td>226</td>
<td>122</td>
<td>+0.5 µ U/mL</td>
<td>0.25</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Singer et al\textsuperscript{23}</td>
<td>20</td>
<td>16</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Albarracin et al\textsuperscript{24}</td>
<td>226</td>
<td>122</td>
<td>-0.54%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>