A systematic review of vanadium oral supplements for glycaemic control in type 2 diabetes mellitus

D.M. SMITH1, R.M. PICKERING2 and G.T. LEWITH1

From the 1Primary Care and 2Public Health Sciences and Medical Statistics, University of Southampton, UK

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Summary

Objective: To assess the effectiveness of oral vanadium supplementation for glycaemic control in type 2 diabetes by conducting a systematic review of the literature.

Design and Methods: Eligible studies were identified by searching 14 databases using standardized terms. Experts, study authors and manufacturers were also contacted. Hand-searching was not undertaken. Selection criteria for inclusion in the review were controlled human trials of vanadium vs. placebo in adults with type 2 diabetes of minimum 2 months duration, and a minimum of 10 subjects per arm. Data extraction, assessment of study quality and outcome analysis were undertaken by two independent reviewers.

Results: One hundred and fifty one studies were found but none met the inclusion criteria. We proceeded to summarize the state of existing evidence and plan for a future clinical trial by applying revised, less restrictive criteria to our search, for clinical trials of 30–150 mg daily oral vanadium supplementation in diabetic humans. Only five were identified. These demonstrated significant treatment-effects, but due to poor study quality, must be interpreted with caution. Treatment with vanadium often results in gastrointestinal side-effects.

Conclusion: There is no rigorous evidence that oral vanadium supplementation improves glycaemic control in type 2 diabetes. The routine use of vanadium for this purpose cannot be recommended. A large-scale randomized controlled trial is needed to address this clinical question.
is not understood.\textsuperscript{3} However, it does have insulin-
mimetic properties in liver, skeletal muscle and adipose tissue in-vitro, and in in-vivo animal models, via inhibition of the phosphotyrosine phosphatase (PTP) enzyme system,\textsuperscript{12,13} thus suggesting it may have a role in glycaemic control.

This systematic review of the available clinical evidence sought to establish whether dietary vanadium supplementation improves glycaemic control in type 2 diabetes mellitus and could be promoted for use in clinical practice. A secondary aim was to identify adverse events associated with vanadium supplementation.

**Research design and methods**

A review protocol was developed with guidance from the Cochrane Metabolic and Endocrine Collaborative Review Group (MECRG).\textsuperscript{14} A questionnaire regarding vanadium supplementation was sent to complementary medicine nutritional experts, and their responses were used to determine real world dose ranges and a minimum duration for effective supplementation.

**Inclusion and exclusion criteria**

The gold standard eligibility criteria for this review were randomized, placebo controlled trials (RCT) of oral vanadyl sulphate, 30–150 mg daily, of at least 2 months duration, with a minimum of 10 adults with diabetes per trial arm. These figures were derived from the nutritional expert’s responses, consideration of likely effect sizes, and the minimum duration of treatment for effects to manifest in the outcome measures. Outcome measures of glycaemic control were HbA1c and fasting blood glucose (FBG).

Given the relatively small scale of complementary medical research it was also acknowledged that less than gold-standard, non-RCT designs might also have something to contribute to the overall analysis. Consequently ‘quasi-RCT’ designs, where a single design criterion was lacking were also included; for example, trials without a placebo control.

**The searches**

As far as possible searches employed the Cochrane Collaboration’s well-validated, highly sensitive MeSH-based ‘diabetes’ and ‘RCT’ search syntax for the major bibliographic databases. Keyword truncations with wildcard characters were used to account for possible derivatives. ‘Medline’ (Ovid), ‘Embase’ (Ovid), ‘Cochrane Central Register for Controlled Clinical Trials’, ‘Cochrane Database of Systematic Reviews’ and ‘Institute of Scientific Information

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clustered analogous terms (truncations omitted for brevity)</th>
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<tbody>
<tr>
<td>Diabetes OR Diabetes Mellitus</td>
<td></td>
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<tr>
<td>Type 1 OR Type I OR Insulin dependent OR IDDM</td>
<td></td>
</tr>
<tr>
<td>Type 2 OR Type II OR Non-insulin dependent OR NID</td>
<td></td>
</tr>
<tr>
<td>Micronutrient OR Supplement</td>
<td></td>
</tr>
<tr>
<td>Vanadium OR Vanadyl OR Vanadate</td>
<td></td>
</tr>
<tr>
<td>Randomized OR Controlled OR Randomized controlled trials OR RCT</td>
<td></td>
</tr>
<tr>
<td>Review OR Systematic</td>
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Science Citation Index’ were searched using these Cochrane, or analogous, syntax and adapted across databases according to their differing facilities. A single set of analogous search terms derived from the Cochrane syntax was applied universally. Table 1 lists the root terms used in the search syntax for every database (truncations are omitted). Complementary and alternative medicine-specific databases and others known to yield unique information were also searched, along with databases of ongoing and/or incomplete trials. The ‘Cumulative Index to Nursing & Allied Health Literature’, ‘Allied and Complementary Medicines Database’, ‘International Bibliographic Info Dietary Supplements’, ‘Institute of Scientific Information Proceedings’, ‘Biosis’, ‘The National Research Register’, ‘Conference Papers Index’, ‘Clinical Trials Register’ and ‘Current Controlled Trials’ were searched. One important database, the Centralised Information Service for Complementary Medicine,\textsuperscript{15} ceased providing searches some months before this review commenced. Language restrictions were not applied, while article references were checked for further examples of relevant research and similarly authors were contacted.

**Paper selection, validity and data abstraction**

The output of these searches was collated and duplications removed within Reference Manager.\textsuperscript{16} The selection of papers for further scrutiny was made by applying the inclusion–exclusion criteria to each title and abstract, a process that was conducted independently by two reviewers. For each selected paper, data were independently abstracted into a modified version of the MECRG’s template data capture form by the two reviewers.\textsuperscript{17} The quality assessment of each selected paper then followed MECRG’s recommendations, by making comparison against evidence-based criteria after Egger et al.,\textsuperscript{18} namely sampling method, randomization, allocation concealment, blinding, identical treatment of
groups, intention-to-treat analysis, and withdrawals, drop-outs and losses being described. Papers were then stratified according to their overall quality as: A (all quality criteria met; low risk of bias), B (one or more criteria only partly met; moderate risk of bias) or C (One or more criteria not met; high risk of bias).19

This stratification set demanding criteria for papers to meet before they could be included in the review: C-level papers were excluded, while the effects of including B-level evidence in the analysis of A-level evidence explored in sensitivity analyses (‘A’ vs. ‘A+B’). A meta-analysis would only be conducted were there sufficient and sufficiently homogenous A-level evidence to make calculating a cumulative statistic reasonable.

Results
Search results
All the databases were initially searched over the course of the week starting 17/1/2005 and yielded 96 papers with an updated search over the week starting 5/11/2007 yielding a further 55 papers. Most of these references were immediately excluded, as they failed to meet the selection criteria. Only five papers were requested for closer inspection. On inspection of the full articles however, it became clear that none of these met the inclusion criteria either. Figure 1 summarizes the process.

Thus this systematic review’s primary finding was that no papers were found that met the inclusion criteria. Consequently this review finds that there is no good evidence that oral vanadium supplementation improves glycaemic control in type 2 diabetes. The routine use of vanadium for this purpose cannot therefore be recommended.

Further questions
Given the lack of high quality evidence, secondary questions arose: ‘What is the existing evidence for vanadium’s clinical effectiveness? Is there a need for an RCT in the near future?’

To address this, the five papers remaining at the penultimate step in Figure 1 were examined, as the ‘closest approximation’ to those originally sought: Namely, any clinical trial of oral vanadium supplementation in adult humans with diabetes. These papers are therefore reviewed here to summarize and critique the currently poor standard of clinical evidence for vanadium in type 2 diabetes.

The existing evidence
None of these five studies meet the original inclusion criteria for this review: They do use prospective, experimental designs, but take a non-randomized, within-subjects approach to provide a degree of experimental control; they are not RCTs or quasi-RCTs; they have too few participants and are of too short a duration; they failed to report some important features.

Table 2 summarizes the design and outcomes assessed in each study. Overall these studies were designed and powered at the level of preliminary trials only. A brief description of the issues with the design peculiarities of each study follows:

Cusi et al.20
Eleven participants with diabetes were subjected to a run-in period followed by an active treatment period. Participants were then followed up after discontinuation of treatment. A parallel group of five participants without diabetes was also observed for the same duration, and not subjected vanadium treatment. The comparison of treatment with no treatment in this study is therefore within-subjects in the diabetic group, and the existence of the non-diabetic, untreated parallel group is never justified.

Halberstam et al. 21
All seven participants with diabetes and all six controls were given active treatment following a run-in period and a placebo period. The main comparison made by this study was therefore between those with diabetes and those without, with vanadium compared to placebo within-subjects only.

Goldfine et al.22
Following run-in and placebo phases three, five and eight diabetics were given different levels of active treatment for a period. Whether these allocations to the differing levels were randomized is not stated. All participants received some level of treatment; there was no control group of untreated diabetics. This more complex design resembles that of a phase II trial to establish therapeutic dose ranges, rather than a clinical effectiveness trial.

Boden et al.23
Eight participants with diabetes were given active treatment for a period then switched to a placebo for a further four weeks. It is not clear whether this switch was blinded, as the remaining six participants are quoted as having (“agreed to continue”). The treatment comparison is within-subjects only and
occurs post-active treatment, with the incumbent high risk of carry-over effects influencing the comparison.

Cohen et al. 24

All six participants with diabetes were given active treatment with before and after placebo periods. Again the comparison of active treatment with placebo is purely within-subjects and risks carry-over effects.

Study outcomes

Table 3 summarizes the means and standard deviations for the measures of glycaemic control
<table>
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<tbody>
<tr>
<td><strong>Age (mean, SD)</strong></td>
<td>59 (2)</td>
<td>53 (2)</td>
<td>53.7 (8.3)</td>
<td>53.5 (2.6)</td>
<td>50.4 (4)</td>
</tr>
<tr>
<td><strong>Groups treated identically</strong></td>
<td>No</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td>n/a</td>
<td>n/a</td>
<td>Unclear</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Not stated</td>
<td>Participant unaware</td>
<td>Participant unaware</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Therapy, route, dose</strong></td>
<td>Oral vanadyl sulphate, titration from 50 mg to 150 mg, as three divided doses (150 mg total daily)</td>
<td>Oral vanadyl sulphate, 50 mg twice daily (100 mg total daily)</td>
<td>Oral vanadyl sulphate, 25, 50 or 100 mg three times daily (75, 150, 300 mg total daily)</td>
<td>Oral vanadyl sulphate 50 mg twice daily (100 mg total daily)</td>
<td>Oral vanadyl sulphate 50 mg twice daily (100 mg total daily)</td>
</tr>
<tr>
<td><strong>Length of run-in, active and placebo periods</strong></td>
<td>4-week run-in phase, 2 weeks titration, 4 weeks full dose</td>
<td>6-week run-in, 2 weeks placebo, 3 weeks active</td>
<td>1-week run-in, 3 weeks of placebo, 6 weeks active</td>
<td>No run-in, 4 weeks of active, 4 weeks placebo</td>
<td>6-week run-in, 2 weeks placebo, 3 weeks active, 2 weeks placebo</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>6-weeks beyond discontinuation of treatment</td>
<td>No follow-up beyond treatment phase</td>
<td>2 weeks beyond discontinuation of treatment</td>
<td>No follow-up beyond vanadyl, switched straight to placebo</td>
<td>No follow-up beyond vanadyl, switched straight to placebo</td>
</tr>
<tr>
<td><strong>Measures of glycaemic control</strong></td>
<td>FBG HbA1</td>
<td>FBG HbA1</td>
<td>FBG HbA1</td>
<td>FBG</td>
<td>FBG HbA1</td>
</tr>
</tbody>
</table>
reported in each study, before and after vanadium treatment. The trend in the majority is an improvement in glycaemic control after vanadium treatment. The $P$-values for each before–after change given in the papers are also present in the table, and indicate that most of the changes are unlikely to have occurred by chance alone.

**Adverse events associated with vanadium**

No serious morbidities were reported, but all studies reported a high incidence of gastrointestinal side-effects which mostly lessened with time. Objective monitoring tests recorded only minor abnormalities in routine kidney, liver and blood screens. No deaths were reported.

**Discussion**

Our searches found no high quality studies: the overall level of methodological quality in the five trials of vanadium in diabetic humans that were examined was low. It would be inappropriate to use the MECRG’s A, B or C quality grading system for RCTs to classify these non-randomized studies. Although each did measure glycaemic control consequent to vanadium treatment, all were essentially uncontrolled cohort studies with all the inherent weaknesses of such designs, and as such failed to achieve the required standard of evidence to recommend the routine clinical use of vanadium.

**The validity of this review**

The majority of the 151 references returned by the searches were narrative review articles, rather than primary research: the number of articles discussing the potential clinical effectiveness of vanadium compounds in type 2 diabetes was substantially greater than those actually presenting any primary evidence. There are several possible reasons for this. First, there could have been a systematic error in this review’s search strategy. However, a wide variety of databases were searched using highly sensitive rather than specific strategies. Every step of the process of search and selection was carried out explicitly, according to an *a priori* method using multiple reviewers.

A second reason for the lack of papers presenting primary evidence may be publication bias, a major concern in many areas of complementary medicine. However the relatively conventional nature of nutritional medicine for type 2 diabetes, and the fact that we were able to identify some experimental designs suggests that other experimental studies would also have been identified by our search strategy, had they existed. It therefore seems unlikely that there are substantial numbers of studies that we failed to identify. Equally, the robust inclusion criteria were essential in assuring the review’s external validity— this is a clinically important question with substantial implications for current practice. Once the lower standards of the revised criteria were employed however, some low quality studies did emerge.

A final reason for the lack of primary evidence is that there is a genuine lack of research in this area, and this seems to us the most likely explanation for the limited number of studies identified.

**Methodological issues with the five ‘Revised Criteria’ studies**

Two of the five studies examined included parallel groups of untreated or non-diabetic participants. These groups do not make for a meaningful

**Table 3** Outcomes before and after vanadium treatment

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Paper</th>
<th>Before (mean, SD)</th>
<th>After (mean, SD)</th>
<th>Reported $P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Cusi <em>et al.</em></td>
<td>8.1 (0.4)</td>
<td>7.6 (0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Halberstam <em>et al.</em></td>
<td>9.4 (0.5)</td>
<td>8.8 (0.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Goldfine, 75 mg</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Goldfine, 150 mg</td>
<td>7.8 (1.7)</td>
<td>6.8 (1.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Goldfine, 300 mg</td>
<td>7.1 (2.3)</td>
<td>6.8 (2.1)</td>
<td>=0.05</td>
</tr>
<tr>
<td></td>
<td>Cohen <em>et al.</em></td>
<td>9.6 (0.6)</td>
<td>8.8 (0.6)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Fasting Blood Glucose (mmol/l)</td>
<td>Cusi <em>et al.</em></td>
<td>10.8 (0.9)</td>
<td>8.6 (0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Halberstam <em>et al.</em></td>
<td>12.3 (1.3)</td>
<td>10.6 (0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Goldfine, 75 mg</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Goldfine, 150 mg</td>
<td>Not stated</td>
<td>Not stated</td>
<td>‘Not significant’</td>
</tr>
<tr>
<td></td>
<td>Goldfine, 300 mg</td>
<td>9.3 (4.0)</td>
<td>8.0 (3.7)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td>Boden <em>et al.</em></td>
<td>9.3 (1.8)</td>
<td>7.4 (1.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Cohen <em>et al.</em></td>
<td>11.7 (1.1)</td>
<td>10.0 (0.8)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
primary comparison of active treatment with placebo, between diabetic subjects. In fact there is no such between-subjects comparison of treatment vs. no-treatment in any of these five studies. Following run-in and placebo periods, each study’s diabetic cohort experience active treatment; there are no parallel groups of diabetic participants receiving placebo. The lack of features such as randomization and parallel control groups renders the evidence from these studies weak.

Small numbers of participants and short durations of treatment further undermine validity of these studies. For example one important measure of glycaemic control, HbA1c, is influenced not only by blood glucose levels but also by the duration of survival of red blood cells in the circulation. Typically red blood cells survive 3 months, so that the turn-over of existing cells would not have resulted in a stable HbA1c in any of the five studies in any of their phases. An underestimation of treatment effects or carry over effects beyond discontinuation of active treatment may have occurred. The rapidity of action of vanadium in bringing about changes in glycaemic control is equally unclear. None of the studies report serial measures during active treatment or washout to address this issue comprehensively.

**Interpreting the outcome measures of the five ‘Revised Criteria’ studies**

Across all five studies most outcomes presented did show a statistically significant improvement over the period of vanadium supplementation. How can these interesting results be interpreted? Unfortunately given the poor quality of these studies, it cannot be assumed that this potentially positive data represents a true therapeutic effect. It could equally be due to bias resulting from patchy reporting; the absence of crucial quality items or random error, given the small group sizes and short duration of treatment. Due to variation in the study designs and their overall lack of quality we did not proceed to a meta-analysis of these data.

**Implications for research**

These five studies amount to early phase work only, but their data are nevertheless interesting because of the size of some of the purported treatment effects. If reproduced in more rigorous and substantial studies, these levels of benefit would represent a clinically important improvement. A sufficiently powered RCT might therefore demonstrate that vanadium is a potentially useful treatment for type 2 diabetes, and this is our main recommendation for future research.

The duration of this trial should be greater than 3 months, in order for changes in HbA1c to become fully apparent. HbA1c is suggested as the primary outcome variable due to its reflection of sustainable, long-term glycaemic control. To determine a suitable trial size, a minimum treatment effect size that would nevertheless still be considered clinically significant is needed. Using the example of Cusi et al., the purported effect of treatment on HbA1c was a reduction of 0.5%, which is certainly of clinical importance. Assuming a trial with 90% power to detect an effect of half this size (0.25%) with slightly larger standard deviation than that reported by Cusi et al. (0.5%) in a 5% two-sided test, 86 x subjects per arm are required. With 10% losses to follow-up, approximately 100 subjects per arm should be recruited.

**Implications for practice**

This review found no high quality evidence to inform in either direction the clinical effectiveness of oral vanadyl sulphate supplementation for glycaemic control in type 2 diabetes. The routine use of vanadium supplementation cannot be recommended in clinical practice as it remains of unproven effectiveness and has side effects. The question of whether its use might contribute to controlling the pandemic of type 2 diabetes mellitus worldwide remains unanswered. On the basis of the existing evidence vendors of vanadium supplements appear to make unwarranted claims for their products.

**Acknowledgements**

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References


