Vanadium in Glucose Metabolism: Past, Present and Future

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Abstract

For over one hundred years it has been known that vanadium exerts an influence on glucose metabolism in humans. Why this influence or effect exists has only been partly elucidated. Furthermore adapting this effect in the treatment of disease has yet to be seized upon successfully. The purpose of this paper is to look at vanadium and its proposed mechanism of action as well as to review many of the pertinent cells, animal and human studies that have been performed and the results obtained in each of these studies. Finally, this review will examine recent published work on vanadium and look at possible future directions.

This review examined all currently published human studies that have so far been performed. Inclusion criteria were that the study had to be performed as an intervention, had to have human patients, and the patients had to have a diagnosis of diabetes either Type 1 or Type 2 with a hemoglobin A1C of 6.5% or greater. Also, measurements such as fasting blood glucose, and hemoglobin A1C had to be obtained both pre- and post-intervention. Exclusion criteria included studies that did not obtain these measurements or where designed to look at bioavailability rather than glycemic control. Results from analyzing previous studies on human populations demonstrated a 0.61% reduction in hemoglobin A1c. This is demonstrated in a forest plot examining selected studies.

Oral vanadium is a potential therapeutic option for the treatment of either Type 1 or Type 2 Diabetes Mellitus in Humans. Human clinical trials have demonstrated both a short term as well as a long term beneficial effect. There is no current human data to suggest that there are any substantial toxicities outside of mild gastrointestinal discomfort. Further studies are needed to address which particular compound holds the most therapeutic potential, and/or to modify these compounds for greater efficacy and less toxicity.

Keywords: Vanadium; Type 1 Diabetes Mellitus; Type 2 Diabetes Mellitus; Micronutrients; Protein tyrosine phosphatase 1B

Introduction

For over a century it has been well-known that the transitional metal vanadium exerts an influence on glucose metabolism in humans [1]. Why this influence exists has only been partly elucidated by work performed over the last three decades [2-4]. Moreover, utilizing this effect in the treatment of disease, while demonstrated in human clinical trials, has yet to be seized upon successfully by either large pharmaceutical companies or small biotechnology startups [5].

Vanadium is a trace element that is found in humans in the earth’s crust. Vanadium, an element from the transition metal group of the periodic table is proposed to be an essential trace element in animals and humans [6,7]. The human body contains 100–200 μg of this element, which is the result of its absorption and excretion [8]. The estimated daily intake of the US population ranges from 10-60 micrograms. Vanadyl sulfate is also a common over the counter supplement that has been used to enhance weight training in athletes at doses up to 60 mg/d [9]. According to the 2001 Institute of Medicine (IOM) Dietary and Nutrition Table on Micronutrients, the tolerable upper limit of normal daily intake for vanadium is 1.8mg though this has not been updated in over 15 years [10].

As mentioned, vanadium has had a long-known association with metabolic effects on glucose predating the 20th century [11]. Interest in this compound and these effects decreased dramatically after the discovery and clinical utility of insulin by Banting and Best in 1922 [12]. However, the treatment of diabetes mellitus and indeed the incidence of DM (diabetes mellitus) did not end with this discovery. Indeed the incidence and prevalence of DM and in particular Type 2 Diabetes Mellitus (T2DM) have never been higher [13].

In the wake of an ever increasing diabetic population more pharmacological therapies have been tested and introduced into clinical practice. These include agents such as metformin, glucagon like polypeptide (GLP-1) agonists, dipeptidyl peptidase (DPP)-4 inhibitors, sodium glucose cotransporter (SGLT-2) inhibitors, among others [14]. Even more drug classes are currently either theorized or in actual development and clinical trial [15,16].

This has led to a renewed interest in vanadium’s long-known effects. Rigorous scientific work elucidating vanadium’s molecular and biochemical effects began in the 1970s and 1980s. In 1979, Tolman et al. demonstrated that in vitro vanadate solutions were shown to possess insulin-like effects on glucose metabolism in rat diaphragms. This study examined multiple vanadium compounds including sodium orthovanadate, sodium metavanadate, ammonium metavanadate, and vanadyl sulfate [17]. Throughout the 1980s many cellular and animal studies were performed. These studies helped conceptualize that vanadium may have the potential as an anti-diabetic agent [18-20]. Successful use and an enhancement of insulin sensitivity in rodents and human diabetic subjects, target these agents preferentially toward T2DM [21].

Cellular and Animal Studies

In 1983, it was characterized by Tamaru et al. the insulin-like effect of vanadate to activate rat adipocyte glycogen synthase, eliminate the inhibition of Na’K’-ATPase or enhanced production of hydrogen peroxide as mechanisms for the insulin-like action of vanadate, and demonstrate that stimulation of the tyrosine kinase reaction is the mechanism of the vanadate enhanced phosphorylation of the subunit of the insulin receptor [22]. In 1985 Heyliger et al. demonstrated that oral administration of sodium orthovanadate to streptozotocin (STZ)-treated diabetic rats normalized the elevated blood glucose after a 4-week period [23].

In 1985, Meyerovitch et al. showed that oral administration of vanadate, under certain experimental conditions, leads to long lasting normoglycemia and a shift from a catabolic state to an anabolic state in STZ-treated rats [24]. In addition, this study also looked at possible toxic effects on both the liver and the kidney and concluded that under certain optimal conditions, vanadate treatment can lead to stable, long lasting normoglycemia, and restore tissue responsiveness to insulin without apparent signs of toxicity [24]. This study also showed that vanadate treatment doubles the basal rate of hexose uptake in both muscle and liver tissues for control and STZ-rats. Finally, this study demonstrated these effects after only a 2-4 day period [24].
In a 1988 cellular study by Solomon et al. it was demonstrated that vanadate stimulates the pentose phosphate shunt to a greater extent than does insulin [2].

In a further study in 1993 on diabetic BB-Wistar rats, by Solomon et al. study they demonstrated that hepatic vanadium levels are not decreased in the SDR (spontaneously diabetic rats) compared to the NDR (nondiabetic rats). The significance of this result is not immediately apparent, but it is not simply a generalized deficiency of this trace mineral in diabetes mellitus, since kidney and muscle levels were unaltered in the SDR compared with the NDR. Although vanadate did not exactly duplicate insulin’s actions, its overall effect on homeostasis results in correction of most of the metabolic abnormalities associated with insulin deficiency [3]. Vanadiums effect has been seen to be enhanced in the setting of increased insulin resistance. Another animal study demonstrated that the insulin requirements of obese rats decreased acutely (within fifteen minutes) over 50% as compared to lean animals [25]. What has not been elucidated in the current literature is the exact molecular ratio of insulin to vanadium. In other words, what would be the insulin equivalent dosage (in Units/kilogram) for a certain dosage of vanadium?

**Human Clinical Trials**

**1993 Soved et al.**

The most recent published clinical trial was also the most long-term study. However, it appears this study may have taken place in the early 1990s even though it was first published in 2013 [26]. This study had a total of 14 patients, all type 1 diabetics who were requiring varying degrees of insulin therapy and also had overall poor blood glucose control. They were maintained on vanadyl sulfate for a total of 30 months. The dosage used was 50-100 mg TID. The daily doses of insulin decreased from 37.2 +/- 5.5 to 25.8 +/-4.6 units/day. Meanwhile, the fasting blood sugar also decreased from 238 +/- 71 to 152 +/- 42 mg/dl (P-value<0.001). This translates to roughly a 30% reduction in the amount of required insulin [26]. It was noted that most of the improvement in fasting blood glucose and insulin requirement occurred during the first 3 months and then was stable for the rest of the study [26]. One interesting piece of data that unfortunately was not obtained in this study was the hemoglobin A1C measurement.

**1995 Cohen et al.**

In this study vanadyl sulfate was administered to 6 Type 2 Diabetic patients for 3 weeks following a 2 week placebo. Another 2 weeks of placebo completed the entire duration (a total of 7 weeks). These patients began with quite poor glucose control with a baseline HbA1C of 9.6%. This corresponded to fasting plasma glucose of 210 mg/dL. After 3 weeks of 100mg/day vanadyl sulfate the A1C improved to 8.1%. Oral vanadyl sulfate 100 mg/day was administered for 3 weeks. The mean HbA1c at the beginning of this study was 10.3%. The amount of decrease in the percent hemoglobin A1C varied by the dosage of vanadyl sulfate. In the 150-mg dose from 7.8% +/- 1.7 to 6.8% +/-1.1. In the 300 mg vanadyl group (7.1% ± 2.3% v 6.8% ± 2.1%, p = .05) mean fasting glucose decreased significantly (167.2 +/-72.9 v 144.1 +/-66.8 mg/dL, p <.02). There was no significant change in weight following vanadium treatment in the group as a whole or in the group receiving the highest administered dose of vanadium [32].

**1996 Boden et al.**

In this study, 8 T2DM patients received oral vanadyl sulfate 100 mg/day for a total of 4 weeks. This study used some patients who were being treated with insulin at the time. The dose of oral vanadyl sulfate was given as 50 mg BID. Treatment with vanadyl sulfate for 4 weeks demonstrated a decrease in blood glucose (mean 9.3 +/-1.8 to 7.4mmol/L; p<0.05) This is close to a 20% decrease in overall fasting glucose. One objective of this study was to examine the effects of vanadyl sulfate on subjects for an extended period. The most common complaint was gastrointestinal discomfort but this seemed to be “transient and disappeared by the end of the first week in all but one patient in whom it lasted for 11 days” [29].

**1996 Halberstam et. al.**

In this study, oral vanadyl sulfate 100 mg/day was administered to a total of 13 patients. Seven of them were type 2 diabetics while the other six were non diabetics. The study utilized a three-hour euglycemic-hyperinsulinemic clamp. This was performed after 2 weeks of placebo and 3 weeks of vanadyl sulfate treatment in the six nondiabetic controls. While decreases in plasma glucose and HbA1c were found in the type 2 diabetics, no changes were seen in the control subjects. In addition, in the diabetic patients, vanadyl sulfate increased the GIR (glucose infusion rate) by 82% indicating increased insulin sensitivity (p<0.05). This increase in sensitivity was felt to be related to suppressed hepatic glucose output. Because, these results were demonstrated in the diabetics only and not the controls the data suggest that vanadyl sulfate may improve a defect in insulin signaling specific to T2DM [30].

**1998 Aharon et al.**

This study had a 5 type 1 DM patients with an average HbA1c of 8.1%. Oral vanadyl sulfate 100 mg/day was administered for 3 weeks. While there were no statistically significant changes found in insulin requirement, weight or appetite, the HbA1c was found to have decreased by 0.5% in just a short time period [31]. The HbA1c after treatment averaged 7.6% in these patients. However, as the authors did not find any other changes in plasma glucose levels they felt that vanadyl sulfate exhibited its effects primarily in patients with insulin resistance [31].

**2000 Goldfine et al.**

This study which was led by the same author of the 1995 study utilized vanadyl sulfate (in place of sodium metavanadate.) The duration of the study was 6 weeks while the total number of patients was 16. Three different dosages were used, 75 mg/day, 150 mg/day and a 300 mg/day. It was felt by the authors of this study that, “vanadyl sulfate appears safe at these doses for 6 weeks” [32]. The mean HbA1c at the beginning of this study was 10.3%. The amount of decrease in the percent hemoglobin A1C varied by the dosage of vanadyl sulfate. In the 150-mg dose from 7.8% +/-1.7 to 6.8% +/-1.1. In the 300 mg vanadyl group (7.1% ± 2.3% v 6.8% ± 2.1%, p = .05) mean fasting glucose decreased significantly (167.2 +/-72.9 v 144.1 +/-66.8 mg/dL, p <.02). There was no significant change in weight following vanadium treatment in the group as a whole or in the group receiving the highest administered dose of vanadium [32].

**2001 Cusi et al.**

This study had a total of 11 patients, all type 2 diabetics that were treated with a 150 mg/day dose of vanadyl sulfate. The duration of the study was for 6 weeks. Treatment significantly (statistically) improved glycemic control. Fasting plasma glucose (FPG) decreased from 194 +/- 16 to 155 +/- 15 mg/dL (p<0.01). Hemoglobin A1c decreased from 8.1 +/- 0.4 to 7.6 +/- 0.4% (p<0.01) [33]. These patients had been treated with sulfonylureas and diet control but none were on insulin therapy. Plasma vanadium levels were determined on the euglycemic insulin clamp days before and after the 6-week treatment period, and 6 weeks after discontinuation of VOSO4 (vanadyl sulfate) treatment.
Fasting plasma vanadium levels were undetectable (<10 mg/L) before treatment and increased to 104 +/-18 mg/L after 6 weeks of VOSO4. Six weeks after discontinuation of VOSO4, levels returned to the undetectable range (<10 mg/L) [33]. Tolerance to vanadyl sulfate was good, as evaluated by history and routine laboratories [33].

2000 Medeval Limited

This study utilized BEOV (bissethylmalto vanadium) complex. Specific objectives were initially to: (1) assess the safety and tolerability of single, escalating dose of orally administered BEOV; (2) determine the pharmacokinetics of modest doses of BEOV; and (3) compare the bioavailability of a well-tolerated dose of oral BEOV and an equivalent molar dose of oral vanadyl sulfate [34]. In total, there were 40 volunteers that were non-diabetic [34]. Initially four volunteers were given a single 10 mg oral dose, open label. This was followed by an escalating dose study, with four dose levels: 25, 35, 60, 90 mg BEOV, four subjects at each dose level and two placebo controls. The third stage was a bioavailability study, in which four volunteers were each given a single 50 mg dose VOSO4, open label [34]. A last phase, looked at the effects of fasting or feeding on bioavailability. In this phase, eight subjects were each given two single 75 mg doses of BEOV, one dose fasted, one fed (non-fasted) in an open-label, randomized, cross-over design [34]. This study was useful for helping to establish bioavailability and pharmacokinetic data but it was not designed to look at glucose metabolism in humans.

2008 Akesis Pharmaceuticals

In this phase IIa clinical trial, BEOV was administered for 28 days to 9 type 2 diabetic patients. The dose used was 20 mg daily. There were associated reductions in HbA1c as well as fasting blood sugar [33]. Over the course of the 28-day treatment period, BEOV was consistently well-tolerated. It was reported that in five out of seven patients the fasting plasma glucose decreased from 10-43%. The HbA1c decreased from 0.3-1.1% [33].

Forest plot

Our forest plot consisted of 5 of the above studies and a total of 47 patients. Using the reported dosages of the oral vanadium compounds the random effects model showed a reduction of HbA1c of 0.61%. The heterogeneity of these studies was 0%, which is an indication of no publication bias and demonstrated in the forest plot seen in Figure 1.

2010 Scior et al.

This study yielded a chimeric design, synthesis, and biological assays of a new nopeptide insulin-mimetic vanadium compound to inhibit protein tyrosine phosphatase 1B [35]. This compound, labeled TSAG0101, shows blood glucose lowering effects in rats but produced no alteration of basal-or glucose-induced insulin secretion on ß cells during in vitro tests, supporting an extrapancreatic mechanism of its effects [35].

2014 Wang et al.

This study examined the vanadium levels in newly diagnosed type 2 diabetics and compared them to nondiabetic controls. In many ways, this study was a human adaptation of the published study by Solomon et al. that looked at vanadium levels in a rat model [3]. In this study it was found that plasma vanadium levels were significantly lower in patients with type 2 diabetes than in the control subjects. The objective was to evaluate the association between plasma vanadium levels and type 2 diabetes. The study design was a case-control study involving 1,598 Chinese subjects with or without newly diagnosed type 2 diabetes (December 2004–December 2007). Mean plasma vanadium levels in participants with and without diabetes were 1.0 μg/L and 1.2 μg/L, respectively. Participants in the highest quartile of plasma vanadium concentration had a notably lower risk of newly diagnosed type 2 diabetes (odds ratio = 0.26, 95% confidence interval: 0.19, 0.35; p<0.001), compared with persons in the lowest quartile [36].

2015 Solomon et al.

This recent study demonstrated that when PTEN (Phosphatase and tensin homolog deleted on chromosome 10) was increased due to Tumor Necrosis Factor alpha treatment the increase was reversible by both PTEN siRNA knockdown and VO-OHpic (a vanadyl compound in complex to hydroxypicolinic acid ) treatment. Thus, PTEN is identified as a potential new therapeutic target for reducing IR (Insulin Resistance) in Type 2 DM [37-38].

5.15 2016 Pirmoradi et al.

The result of this study indicated that the mechanisms of insulin-like activity of vanadium improved glucose homeostasis in STZ-diabetic rats. Furthermore, the insulinitropic activity of vanadium stimulated beta-cell proliferation and replaced the damaged insulin secretory cells, and the relief of glucose toxicity happened in vanadium or insulin-treated diabetic rats had a minimal role in this accomplishment [39].

This study supports prior pharmacological interventions that effectively stabilize a functional beta-cell mass at the onset of Type 1 diabetes have been shown to induce a chronic amelioration of the

Figure 1: Forest Plot depicting the HbA1c reduction on a combined 7 human trials. The overall estimate for HbA1c reduction is estimated to be -0.61%.

diabetic state. The degree of beta-cell protection afforded by vanadium, to the extent that some treated animals experience a chronic reversal of the diabetic state, may depend on the relative number of beta cells that initially survived destruction by STZ [40].

This notion of a complementary action between vanadium and insulin is inherent in the observation that more severely diabetic animals, which had a lower residual pancreatic insulin content at 5 weeks, also required higher concentrations of vanadium to achieve normoglycemia [41]. However, although the effectiveness of vanadium is initially dependent on the residual insulin stores, when administered at higher concentrations it can elicit normoglycemia even in animals with insulin stores as low as 2.5% of control [40]. As beta-cell function in STZ-diabetes is very closely correlated with pancreatic insulin content, it would mean that vanadium could continue to exert its glucose lowering effects even when pancreatic secretory function is severely diminished [40] (Tables 1 and 2).

### Toxicology Concerns

At this time, there appears to be conflicting results in regards to side effects. More recently, it was shown that organic vanadium compounds were much safer than inorganic vanadium salts and did not cause any gastrointestinal discomfort, hepatic or renal toxicity [45]. In several sub-acute studies on animals, vanadium deficiency compounds were much safer than inorganic vanadium salts and did not cause any gastrointestinal discomfort, hepatic or renal toxicity [41]. However, although the effectiveness of vanadium is initially dependent on the residual insulin stores, when administered at higher concentrations it can elicit normoglycemia even in animals with insulin stores as low as 2.5% of control [40]. As beta-cell function in STZ-diabetes is very closely correlated with pancreatic insulin content, it would mean that vanadium could continue to exert its glucose lowering effects even when pancreatic secretory function is severely diminished [40] (Tables 1 and 2).

### Table 1: Characteristics of Human Clinical Trials.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>11</td>
<td>10</td>
<td>7</td>
<td>16</td>
<td>8</td>
<td>6</td>
<td>14</td>
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<tr>
<td>Age (mean)</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Groups</td>
<td>11 Type 2 diabetics and 5 type 1 diabetics</td>
<td>7 Type 2 diabetics</td>
<td>16 Type 2 diabetics</td>
<td>8 type 2 diabetics</td>
<td>6 type 2 diabetics</td>
<td>14 Type 1 diabetics</td>
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<tr>
<td>Placebo-Controlled</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Randomization</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Blinding</td>
<td>No</td>
<td>No</td>
<td>Participant Unaware</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Therapy</td>
<td>Oral Vanadyl Sulfate 50mg TID (Total Daily Dose 150mg)</td>
<td>Oral Sodium Metavanadate 125mg/day</td>
<td>Oral Vanadyl Sulfate 50mg BID</td>
<td>Oral Vanadyl Sulfate 25mg, 50mg or 100mg TID. TDD of 75mg, 150mg or 300mg</td>
<td>Oral Vanadyl sulfate 50mg BID (100mg daily)</td>
<td>Oral Vanadyl sulfate 50mg BID (100mg daily)</td>
<td>Oral Vanadyl Sulfate 50-100mg daily</td>
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<tr>
<td>Trial Length</td>
<td>4 Weeks Run in, 2 weeks titration, 4 weeks full dose.</td>
<td>2 weeks</td>
<td>6 week run in, 2 weeks placebo, 3 weeks active</td>
<td>1 week run in, 3 weeks of no placebo, 6 weeks active</td>
<td>No run in, 4 weeks active, 4 weeks placebo</td>
<td>6 week run in, 2 weeks placebo, 3 weeks active, 2 weeks placebo</td>
<td>30 months</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>6 weeks beyond discontinuation of treatment.</td>
<td>None</td>
<td>2 weeks of discontinuation beyond treatment</td>
<td>No follow-up</td>
<td>No follow-up</td>
<td>No follow-up</td>
<td>3 months</td>
</tr>
<tr>
<td>Measures of Glycemic Control</td>
<td>FBG, HbA1c</td>
<td>FBG, HbA1c</td>
<td>FBG, HbA1c</td>
<td>FBG, HbA1c</td>
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<td>FBG, HbA1c</td>
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### Future Potential

After more than thirty years of research, vanadium has consistently demonstrated positive results on glucose metabolism. This has been demonstrated at the cellular level, at the animal model level and in small but statistically significant human studies. It must be noted that in spite of the positive effects of the human clinical trials reported these were very small trials with mostly very short time periods. While these studies produce statistically significant results, they are however, not clinically significant. At pharmacological doses, vanadium compounds display relevant biological actions such as insulin and growth factor mimetic or enhancing effects [45]. In spite of this, vanadium has not made it into the mainstream armamentarium of diabetes medications. This is due to the limitations of the human trials having very few subjects and all of them (except the 30 months in the Soved study) lasting on average 4-6 weeks.
This was aptly pointed out in a recent publication by Scior et al. [5]. These studies open therapeutic possibilities in diabetes, particularly, in states of insulin resistance [46]. The combination of vanadium complexes with other compounds may offer an alternative mechanism for its use. This was recently demonstrated in a study where vanadium was complexed with metformin [47]. Another recent study also looked at vanadium’s effect when complexed with rosiglitazone [48]. These studies demonstrate another way that vanadium may yet exert a potential benefit as an antidiabetic agent. As pointed out a sufficiently powered randomized controlled trial might therefore demonstrate that vanadium is a potential treatment for type 2 diabetes, and this is our main recommendation for future research [49]. The current data would imply that vanadium would be used mostly as adjunctive therapy rather than as solo therapy [50]. As more details of vanadium’s bio-distribution in vivo are forthcoming, individualized treatment regimens may become possible optimizing the performance of any given vanadium pharmaceutical agent [4]. There may even be potential for vanadium to be used in medicinal applications beyond diabetes [51,52].

### Reference


### Table 2: Summary of Study Results.

<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>
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</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Cusi et al. [34]</td>
<td>8.1 (0.4)</td>
<td>7.6 (0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Goldfine et al. [28]</td>
<td>9.4 (0.5)</td>
<td>8.8 (0.5)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Halberstam et al. [30]</td>
<td>75mg</td>
<td>7.8 (1.7)</td>
<td>6.8 (1.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Goldfine et al. [32]</td>
<td>150mg</td>
<td>7.1 (2.3)</td>
<td>6.8 (2.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cohen et al. [27]</td>
<td>9.6 (0.6)</td>
<td>8.8 (0.6)</td>
<td>&lt;0.002</td>
<td></td>
</tr>
<tr>
<td>FBG (mmol/l)</td>
<td>Cusi et al. [34]</td>
<td>10.8 (0.9)</td>
<td>8.6 (0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Goldfine et al. [28]</td>
<td>12.3 (1.3)</td>
<td>10.6 (0.9)</td>
<td>&lt;0.09</td>
<td></td>
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<tr>
<td>Halberstam et al. [30]</td>
<td>75mg</td>
<td>9.3 (4.0)</td>
<td>8.0 (3.7)</td>
<td>&lt;0.02</td>
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<tr>
<td>Goldfine et al. [32]</td>
<td>150mg</td>
<td>9.3 (1.8)</td>
<td>7.4 (1.4)</td>
<td>&lt;0.05</td>
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<td>Cohen et al. [27]</td>
<td>11.7 (1.1)</td>
<td>10.0 (0.8)</td>
<td>&lt;0.05</td>
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<tr>
<td>FBG (mg/dl)</td>
<td>Sovied et al. [26]</td>
<td>238 (71)</td>
<td>152 (42)</td>
<td>&lt;0.001</td>
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<td>Sovied et al. [26]</td>
<td>13.3 (3.9)</td>
<td>8.43 (2.39)</td>
<td>&lt;0.001</td>
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