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EFFECTS OF VANADIUM COMPOUNDS ON GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS: A META-ANALYSIS OF COMPARATIVE STUDY ON RATS

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ABSTRACT

Aim: To assess the effect of vanadium compounds on glycemic control in diabetic rats.

Methods: Eligible studies were identified by searching two databases; one search engine was also used for search of articles from different data bases using standardized terms and Boolean logic. Statistical analysis was performed with Meta Analyst software.

Results: 56 relevant studies were found but only 8 studies met the inclusion criteria for this meta-analysis. Meta-analysis was done for blood glucose level from a pooled sample of 84 vanadium treated and 80 control diabetic rats. The analysis generated a combined standardized mean difference (Std. mean difference) of -5.21 and $p< 0.00001$ for blood glucose level. Additionally, all the included studies lay in favor of vanadium treatment. The meta-analysis for average weight and plasma insulin level did not show significant variation between vanadium treated and control diabetic rats.

Conclusion: This meta-analysis reaffirmed that, vanadium compounds are able to reduce significantly blood glucose level and other base line measures like food intake and fluid intake without affecting plasma insulin level and average weight.

INTRODUCTION: Diabetes mellitus is a group of chronic metabolic disorders characterized by persistent hyperglycemia that may result in long-term microvascular, macrovascular, and neuropathic complications [1, 2]. In Ethiopia, community based studies are non-existent at the national level; as a result, the national estimate is based on neighboring country (Sudan) with similar socio-economic situations and accordingly, 2-3% of the population is estimated to live with diabetes [3].

Diabetes mellitus is found to be the leading cause of end-stage renal disease, non traumatic lower extremity amputations, and adult blindness in the USA [2].

The number of people who are diabetic is increasing; which is mainly attributed to aging, urbanization, obesity and physical inactivity [4]. From the world population, 2.8% was diagnosed to have diabetes in 2000 and it is estimated to be doubled in 2030 [4].

On the basis of the pathogenic process that leads to hyperglycemia, diabetes mellitus is grouped in to two broad categories: type 1 and type 2 [2]. Type 2 accounts for as much as 90% of all cases of DM [1] and the incidence in Africans aged above 40 was 2.9% in 2008 [5]. Type2 is very common in all ethnic groups other than Caucasians [6]; moreover, black Central Africans have 2–10 times higher risk than Caucasian & Asians [4].

Two of the major goals of diabetes therapy are to reduce hyperglycemia and body weight [7]. Studies on diabetes have progressed exponentially over the last two decades and have contributed volumes to our understanding of the complex inter-relationship between insulin action, insulin resistance, and lipid and carbohydrate metabolism [8].

From studies on diabetes, the identification of vanadium salt as glucose lowering agent [9] has revolutionized the search for new drug that could mimic insulin. Vanadium compounds were shown to: lower blood glucose level [10], stimulate glucose uptake [11] and increase glucokinase and hexokinase activity as well [12]. The compounds of Vanadium, in general, fall into three major categories: inorganic vanadium salts (vanadate and vanadyl), peroxo vanadium complexes, and organic vanadium compounds [13].

For several years, inorganic vanadium compounds, such as sodium orthovanadate and vanadyl sulfate, were used in both animal and human studies. Although these compounds were shown to be glucose-lowering agents, their exaggerated side effects, mainly gastrointestinal discomfort, limited their use as therapeutic agents [14]. The effective glucose-lowering doses of sodium orthovanadate and to a lesser extent vanadyl sulfate produce diarrhea and dehydration [14]. In contrary to inorganic vanadium compounds, organic vanadium compounds found to have a high rate of absorption [15, 16], improved bioavailability and reduced side effects [15, 16]. Moreover, organic compounds of vanadium found to have better quality in potency, toxicity profile, and tolerance [17].

Even though there are ample of studies done on the role of vanadium compounds in preventing hyperglycemia, to the best of our knowledge, no meta-analysis has been done ahead of this analysis. We conducted meta-analysis on the effect of vanadium compounds on glycemic control in diabetic rats by focusing on blood glucose level, food intake, fluid intake, weight gain and plasma insulin level.

METHODS

Literature search strategy: The databases which were searched for literatures were Medline and hinari; in addition to these data bases, articles were searched from different data bases with the help of Google scholar search engine. The computer-based search strategy included common text words (like vanadyl, vanadate, orthovanadate etc), medical subject headings related to vanadium and type2 diabetes and combining common text words with medical subject headings with the help of Boolean logic.

Inclusion criteria: The inclusion criteria include:

1) Articles written in English and;

2) Articles containing mean and standard deviation (or standard error) of blood glucose level.

Criterion 1 was set because the authors cannot read articles written in other languages and Criterion 2 was set because blood glucose level was the key measurement in this meta-analysis.

Data extraction: The following data were extracted from the articles: sample size and post intervention means ± SDs or SEs for the vanadium treated and controlled rats with type 2 diabetes. For studies which reported SEs rather than SDs, SD was calculated using the formula;

$$SD = SE \times \sqrt{n}$$

Where n is the sample size.

Results which were given as mol/l were changed to g/ml for blood glucose level and plasma insulin level by taking 180g and 5808g as the molecular weight of glucose and insulin, respectively.

Statistical Analysis: Statistical analysis was performed with Meta Analyst (Beta 3.13) software. In each study, the effect size for the intervention was calculated by the difference between the means of the vanadium treated and control groups at the end of the intervention. Each mean difference was weighted according to the inverse of its variance (IV), and then the average was taken (standardized mean difference [Std.MD]).

When significant heterogeneity was found from the test for heterogeneity, the random-effects model was used rather than the fixed effect model.

RESULTS: The initial search identified a total of 56 full journal articles. After reviewing the titles and abstracts of all the 56 articles, 16 studies were accepted for further screening, and the complete papers of these studies were then reviewed in detail. Of these, 8 studies fully met inclusion criteria and were included in the meta-analysis. The most common reasons for exclusion were: review article only, in vitro studies, lack of type 2 diabetic control groups and inability to extract exact values from graphs. In all studies, rat models for diabetes mellitus were developed by injecting Streptozotocin (STZ). As shown in **table 1**, six of the studies used Wistar rats and the remaining two used Sprague-Dawley rats as rat models for diabetes mellitus.

TABLE 1: BACKGROUND INFORMATION ON STUDIES SELECTED FOR THIS META ANALYSIS

Author	Rat strain	Sex	Vanadium compound	Treatment Duration
Valera A *et al* [18]	Sprague-Dawley rats	M	Sodium orthovanadate	2 days
Ramachandran B *et al* [19]	Wistar rats	M	Macrocyclic binuclear oxovanadium	4 weeks
Gil J *et al* [20]	Sprague-Dawley rats	M	Sodium orthovanadate	2 weeks
Mcneill J H *et al* [9]	Wistar rats	F	Sodium Vanadate	4 weeks
Marzban L *et al* [21]	Wistar rats	M	bis(maltolato), oxovanadium(IV)	4 weeks
Amessou M *et al* [22]	Wistar rats	M	Sodium Vanadate	18 days
Blondel O *et al* [23]	Wistar rats	F	Sodium metavanadate	3 weeks
Sun Q *et al* [24]	Wistar rats	M	Sodium Vanadate	----------

The standardized mean difference for the individual study and meta-analysis for blood glucose level were calculated from a pooled sample of 84 vanadium treated and 80 controls. The heterogeneity test uncovers significant variation among studies (I^2 = 86.4%). seeing that random effect model was used for meta-analysis and generated a combined standardized mean difference (Std. mean difference) of -5.21, 95% confidence interval (CI) (-6.93, -3.49) and P < 0.00001; all studies lay in the favour of vanadium treatment (**Fig. 1**).

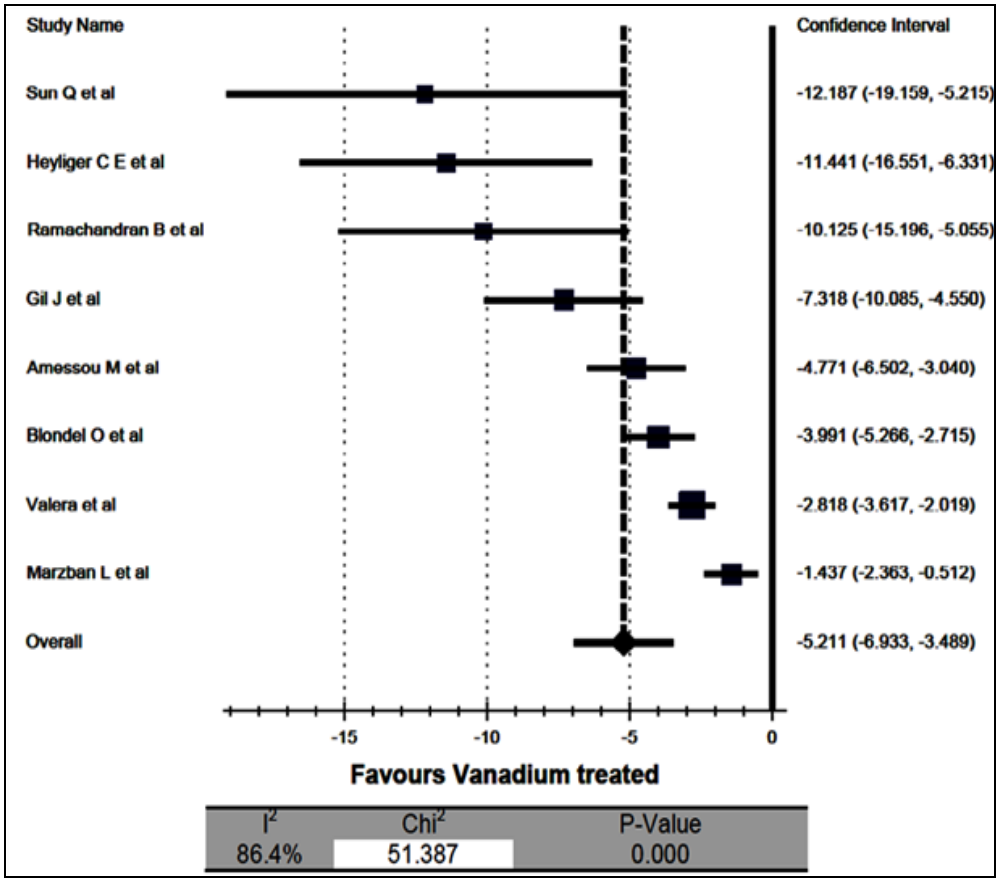

FIG. 1: META-ANALYSIS OF VANADIUM TREATMENT ON RATS' BLOOD GLUCOSE LEVEL: EIGHT COMPARATIVE STUDIES

The standardized mean difference for the individual study and meta-analysis for food intake were determined from a pooled sample of 29 vanadium treated and 22 control diabetic rats. Heterogeneity was found between studies by heterogeneity test; thus a random effect model used for meta-analysis. The analysis generated a combined standardized mean difference (Std. mean difference) of -2.84, 95% confidence interval (CI) (-5.49, -0.19) and p=0.04; all studies lay in the favour of vanadium treatment **(Fig. 2)**.

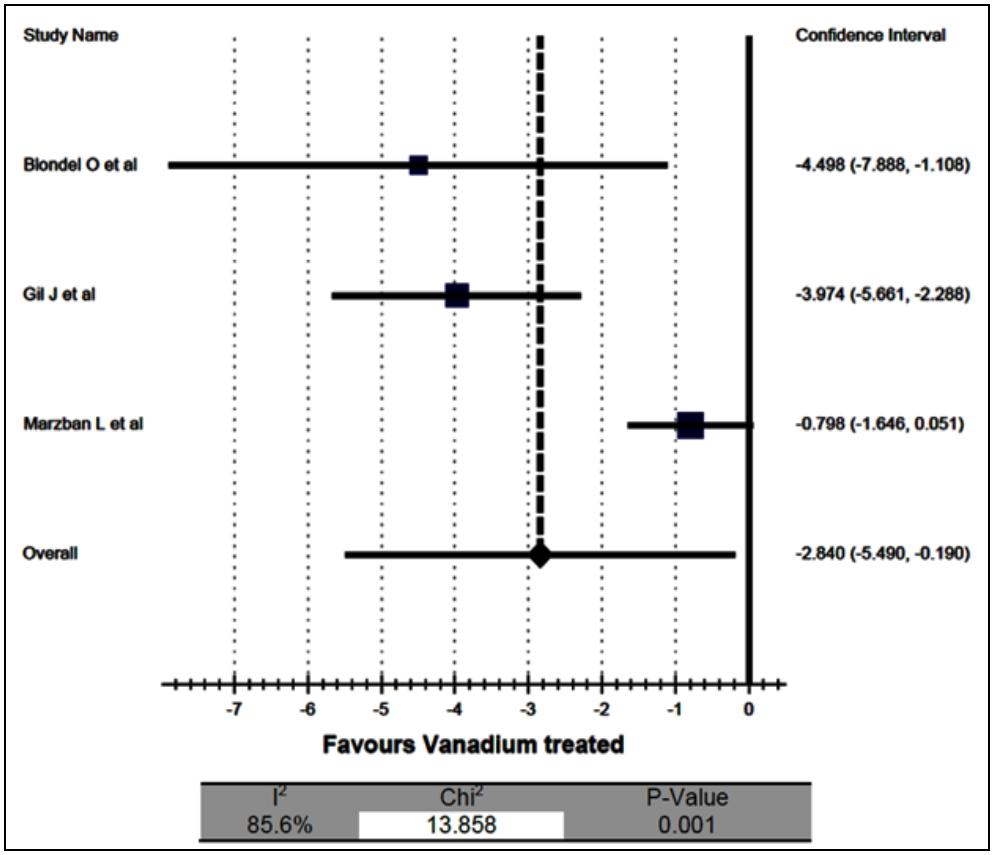

FIG. 2 META-ANALYSIS OF FOOD INTAKE OF DIABETIC RATS AFTER INTERVENTION

As presented in **Fig. 3**, the forest plot of standardized mean difference for the individual study and meta-analysis for fluid intake was plotted from a pooled sample of 62 vanadium treated and 53 control diabetic rats. The heterogeneity test reveals significant variation among studies; as a result a random effect model used for meta-analysis and generated a combined standardized mean difference (Std. mean difference) of -4.16, 95% confidence interval (CI) (-5.86, -2.46) and p<0.00001 for fluid intake; all studies lay in the favor of vanadium treatment.

The forest plot of standardized mean difference for the individual study and meta-analysis for average weight was plotted from a pooled sample of 73 vanadium treated diabetic rats and 69 controls (**Fig. 4**). Heterogeneity was found between studies by heterogeneity test. A random effect model was applied for meta-analysis and generated a combined standardized mean difference (Std. mean difference) of -0.22, 95% confidence interval (CI) (-1.49, 1.05) and p=0.73. Four of the studies favor the control groups but two of the studies favor the vanadium treated group.

Fig. 5 presents the forest plot of standardized mean difference for the individual study and meta-analysis for plasma insulin level from a pooled sample of 62 vanadium treated and 61 controls. The heterogeneity test unveiled significant variation among the studies; accordingly meta-analysis was performed with random effect model and generated a combined standardized mean difference (Std. mean difference) of 0.93, 95% confidence interval (CI) (-0.14, 2.00) and p=0.09. Three of the studies favor control groups, one study favors vanadium treatment and the remaining one does have zero value (in between).

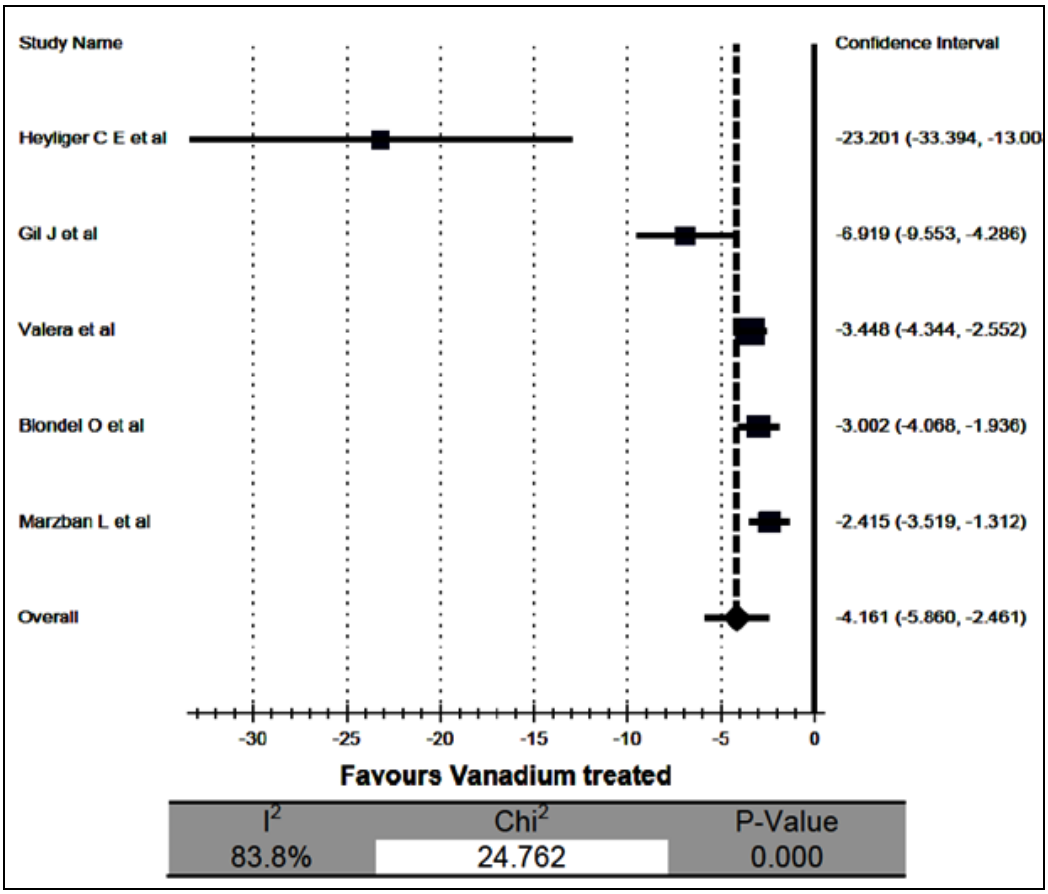

FIG. 3: META-ANALYSIS OF FLUID INTAKE OF DIABETIC RATS AFTER INTERVENTION

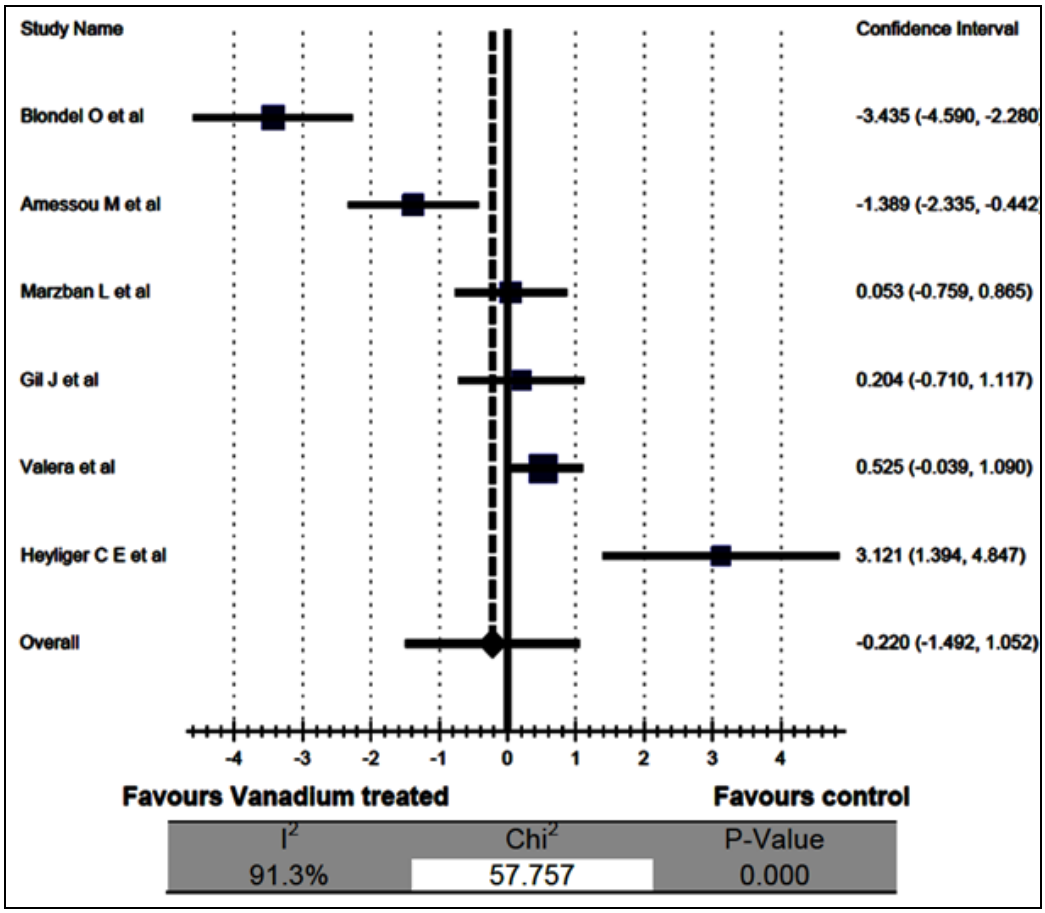

FIG. 4: META ANALYSIS OF AVERAGE WEIGHT CHANGE OF DIABETIC RATS AFTER INTERVENTION

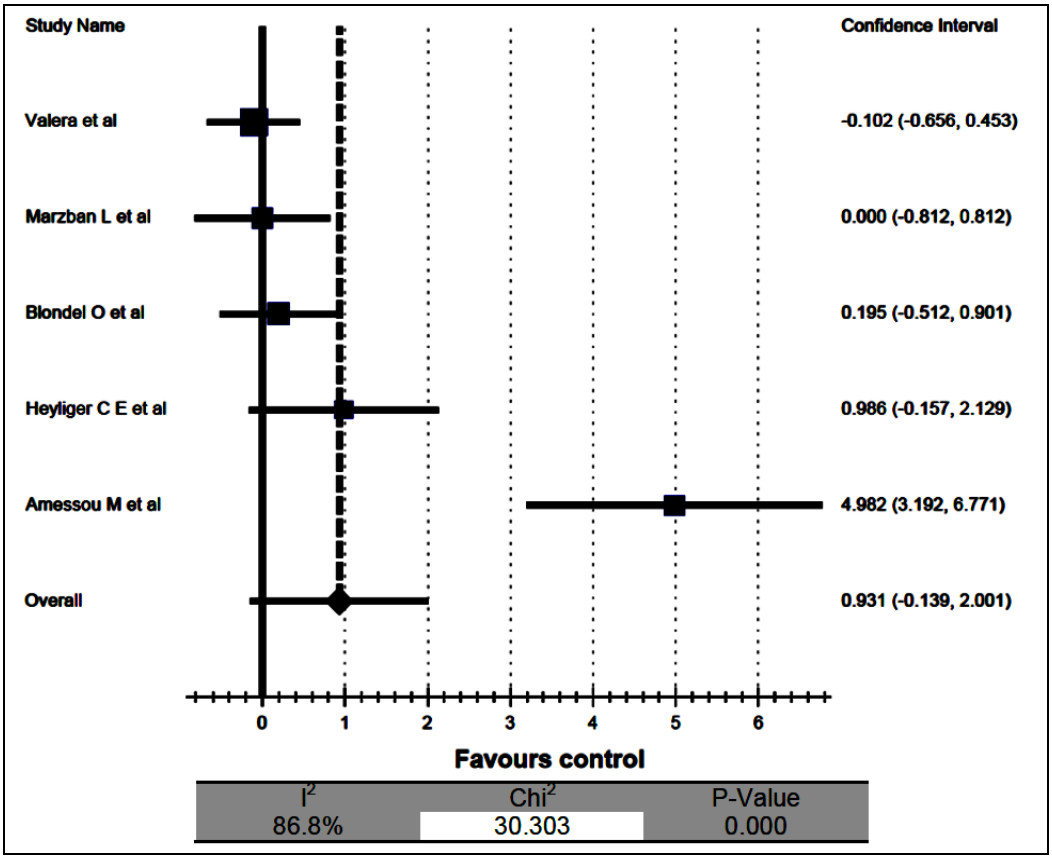

FIG. 5: META-ANALYSIS OF PLASMA INSULIN LEVEL OF DIABETIC RATS AFTER INTERVENTION

DISCUSSION: Since the proposition of vanadium as an orally active glucose lowering agent [9], many subsequent replication studies had shown strikingly consistent results in *in-vitro* tests [25, 26], different animal models [27, 28] and some human trials [29, 30].

Given that diabetes mellitus is characterized by persistently increased blood glucose level [1, 2], increased intracellular glucose level in sequence leads to formation of advanced glycosylation end products via the non-enzymatic glycosylation of intra- and extracellular proteins [2]. Glycosylation of proteins guides to secondary complications of diabetes mellitus like: cataract formation, retinopathy, neuropathy and nephropathy [2].

A prior study showed, a well-controlled blood glucose level, reduces risks of microvascular and neurological complications of diabetes mellitus [31]. Irrespective of the rat strains, sex of the rats and vanadium compounds used, the result from this meta-analysis showed improved glycemic control among vanadium treated rats. The mean blood glucose level was significantly lower in vanadium treated diabetic rats than the controls.

Besides the improvement of elevated blood glucose level in vanadium treated rats, the meta-analysis for food intake and fluid intake also revealed significant variation between vanadium treated and control diabetic rats i.e. The food and fluid intake were much lower in the vanadium treated diabetic rats than controls. Since Polyphagia and polydipsia are among the cardinal sign and symptoms of diabetes mellitus [2], the meta-analysis noted that vanadium compounds are good enough in averting sign and symptoms of diabetes mellitus.

One of the major short coming from most of the existing drugs for type 2 diabetes mellitus therapy is weight gain [1]. But the meta-analysis of vanadium compounds effect on average weight doesn't brought significant average weight variation between vanadium treated and control diabetic rats. This may possibly make vanadium the promise of future type 2 diabetes mellitus therapy by avoiding the short comings of the existing therapies. The currently existing drugs for diabetes mellitus act by enhancing the secretion of insulin or sensitizing the body for the insulin action or reducing the absorption of glucose from the small intestine.

In contrast to insulin secretion enhancers, the results from this meta-analysis point up an improved glycemic control, reduced food intake and fluid intake among vanadium treated diabetic rats without significant variation of plasma insulin level from controls. This may foster the propositions that vanadium compounds acts like insulin (mimic) by their own without the need of insulin. Some of the propositions for vanadium compounds: vanadium compound act independent of insulin [32], Vanadium compound activate adipocyte glycogen synthase similar to insulin [33], Vanadium compound restores glucose 6-phosphate [24] etc.

This meta-analysis noted high degree of heterogeneity with the mean differences of blood glucose level, fluid and food intake, average weight and plasma insulin level across the eight included articles. The possible explanations for the inconsistencies across studies might be that, the discrepancy in dose of vanadium compounds along with studies, the variation in duration of therapy, the difference in the time of blood glucose determination, the time gap between STZ-injection and start of vanadium therapy, the dissimilarity in the sex of the rats, the disparity in the age of the rats, the difference in the rats strain, the variation in the vanadium compounds used for therapy across studies.

In conclusion, the results from this met-analysis reaffirmed that, vanadium compounds are able to reduce elevated blood glucose level significantly and other base line measures like food intake and fluid intake without affecting plasma insulin level and average weight of diabetic rats. In humans the number of studies is quite few, future studies are expected to address the long term safety, efficacy and potency of vanadium compounds on humans.

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