ORIGINAL ARTICLE

Effects of adjunct therapy of a proprietary herbo-chromium supplement in type 2 diabetes: A randomized clinical trial*

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Background: Chromium chelates/complexes are widely used as nutritional supplements to redress complications of type 2 diabetic mellitus (T2DM) patients. However, most of these chelates could be susceptible to oxidation into toxic Cr(VI) state. Complexation of Cr (III) with gallo-ellagi tannoids produces a herbochromium supplement (HCrS) that maintains its Cr3+ oxidation state under oxidizing circumstances *in vitro*. It was tested with conventional oral hypoglycemic drugs [(oral antidiabetic drugs (OAD)] for its beneficial effects in T2DM patients. **Objective:** A randomized clinical study with three OADs with or without HCrS was carried out in T2DM patients to evaluate the efficacy of the HCrS supplement. **Materials and Methods:** 150 T2DM patients were randomized into six treatment groups. After 60 days of treatment, fasting blood glucose and post-prandial blood glucose (FBG and PPBG, respectively), HbA_{1c}, HsCRP, oxidized low density lipoprotein (LDL), and urinary microalbumin levels and other diabetic symptoms were evaluated. **Statistical Analysis:** Findings were compared using one-way analysis of variance (ANOVA) with *post hoc* pairwise comparisons of groups using the least significant difference method. **Results:** Better control of FBG and PPBG levels were observed in patients receiving HCrS (–12.4 to –16.6%) compared to placebo groups (–3.4 to –9.4%). There was a 5.5–7.4% decrease in HsCRP and LDL levels in patients receiving HCrS, which is better than placebo treated groups. Significant decrease in urinary microalbumin level was observed in patients receiving HCrS (–20.0 to –22.5%) compared to placebo groups (–7.8 to –11.6%). Significant decreases in diabetic symptoms were observed in patients receiving HCrS (–47.4 to –59.4%) compared to that observed in placebo groups (–18.0 to 34.0%). **Conclusion:** The findings indicate that HCrS with OAD improves overall diabetic complications within 2 months and may be useful in long-term therapy.

KEY WORDS: Antidiabetic clinical study, fasting and postprandial blood glucose levels, HbA_{1c}, herbo-chromium supplement, HsCRP

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive syndrome which is the sixth leading cause of death and is a contributory factor in many other morbidities and mortalities.[1,2] Rapid urbanization and change of lifestyle have led to a steady increase of T2DM worldwide, particularly in developing countries.[3] With the advancement of oral hypoglycemic drugs [(oral antidiabetic drugs (OAD)], most of these patients control the hyperglycemia satisfactorily; however, attempts are continuously made in search of alternative treatments directed toward improving insulin sensitivity. In the mid-20th century, chromium has been described as 'glucose tolerance factor'.[4] Numerous studies on the physiology of chromium deficiency, the effects of chromium supplementation and probable mode of action have been carried out in the last 40 years.[5-7] Several well-controlled clinical trials using chromium supplement to influence the manifestation of T2DM have shown improved

glucose tolerance, decreased plasma glucose, decreased total cholesterol: high density lipoprotein (HDL) ratio; however, some other studies have indicated no observable beneficial effects to justify its use as supplements.[8,9] One of the cogent reasons for such conflicting results was the complexity of chromium metabolism within the body and in the determination of systemic oxidation status of chromium status of an individual.[6] Cr (III) complexes including Cr (III) picolinate could be oxidized to Cr (VI) by H_2O_2 in neutral aqueous solutions. Cr (III) complexes with serum proteins, such as albumin and transferrin, could also be oxidized to Cr (VI) under similar conditions.[10] Chromium supplements have also been shown to induce chromosome damage and tend to accumulate in human tissues when consumed in high doses for prolonged period of time.[11,12] Deleterious effects of chromium supplements may occur from its ligand [11] or its higher than trivalent oxidation state.[13]

The risk factor of hexavalent chromium induced toxicity has been avoided by using trivalent chromium complexed with an appropriate antioxidant ligand, *Phyllanthus emblica* (amla) fruit extract, which not only possesses strong antioxidant activity but has also been used for thousands of years in Ayurveda as medicine, as well as food, without any toxic manifestations. Complexation with gallotannoids, the active and most abundant ingredients of amla,[14] improved bio-absorption, water-solubility and thus avoided undesired accumulation of chromium in tissues. Addition of purified Shilajit containing oxygenated dibenzo-alpha-pyrone (DBP) and its conjugates and fulvic acids improved the bioavailability of chromium at its target sites.[15] The dried, free flowing sample was designated as a herbo-chromium supplement (HCrS). This study was aimed at evaluating antidiabetic activity of HCrS when administered as an adjunct therapy with oral hypoglycemic drugs (OAD), viz., glipizide, metformin and pioglitazone.

Materials and Methods

Preparation of the drug

A water solution of $CrCl_3.6H_2O$ (one part) was prepared with rapid stirring. Amla fruit extract (three parts), procured from Indian Herbs, Saharanpur, India, was mixed with that solution and stirred for another 30 minutes. Processed Shilajit[15] (three parts) and microcrystalline cellulose (MC; three parts) were added to the same solution and stirred for another 30 minutes. In the final preparation, $CrCl_3.6H_2O$:amla fruit extract:processed Shilajit: MC remains in a proportion of 1:3:3:3. The mixture was evaporated in a rotary vaccum evaporator below 45°C. A blackish-green colored solid was obtained which was designated as HCrS and was desiccated. A voucher specimen is kept in the laboratory with specific code number NC0307. Then 10 mg of HCrS powder containing 200 μg of chromium was further formulated using 240 mg of MC and packed in hard gelatin capsules.

Purity of the drug

Purity of HCrS was established by comprehensive chromatographic and spectroscopic analyses of the complex. Contents of amla and Shilajit were determined by HPLC-PDA technique and were compared with the calculated values of these components in the complex. Chromium content was determined by atomic absorption spectroscopy (AAS). Content of MC was determined by gravimetric method after dissolution of HCrS in water and recording the residual solid content.

HPLC conditions for determination of amla components are as follows.

- Column: NovaPak RP C18 (150 × 3.9 mm, 4 μm) (Waters);
- mobile phase: 0.1 M aqueous sodium acetate solution (pH 3.9);
- flow rate: 0.6 ml/minute (isocratic mode) and
- detection: PDA 280 nm.

HPLC conditions for determination of Shilajit components are as follows.

- Column: NovaPak RP C18 (150 × 3.9 mm, 4 μm) (Waters);
- mobile phase: water:acetonitrile:orthophosphoric acid 67:32:1 (v/v/v);
- flow rate: 0.7 ml/minute (isocratic mode) and
- detection: PDA 240 nm.

The conditions for AAS of chromium are as follows: Samples were extracted with a mixture of 3% aqueous Na_2CO_3 and 1% aqueous NaOH, vortexed and sonicated for 10 minutes. Then the samples were acidified and analyzed for chromium content by AAS. The analyses were performed in triplicate in a Varian SP-20 BQ atomic absorption spectrophotometer. Standard chromium solution was prepared with $K_2Cr_2O_7$.

Reproducibility of the synthesis

Reproducibility of the synthesis of HCrS was confirmed by analysis of the chromium content of three batches of the sample by AAS. Method of sample preparation and conditions for AAS analyses were similar to those

mentioned above.

Evidence in support of maintenance of Cr3+ oxidation state under oxidizing circumstances

HCrS sample containing Cr3+ was dissolved in water (10 mg in 1 ml) and treated with excess ammonium persulphate (four times w/w than that of sample) (oxidant) and silver nitrate as a catalyst (0.5 mg). The mixture was heated in a steam bath for 5 minutes. The product was acidified with conc. sulfuric acid to which 200 µl of 1,5 diphenyl carbazide (0.5% w/v in acetone) was added. The volume of this product was made upto 2 ml with distilled water and its absorbance was determined at 540 nm in a JASCO V-530 dual beam spectrophotometer [Figure 1].

Selection of the patient

The clinical trial was conducted between December 2005 and December 2007 at J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata, India, after obtaining necessary permission from Institutional Ethics Committee (IEC) and approval of the protocol by the Scientific Review Committee (Ayurveda), Government of West Bengal. The IEC did not permit inclusion of any group receiving only HCrS in this study, considering the risk of hyperglycemia in T2DM patients. Patients receiving oral hypoglycemic drugs for no more than 5 years were initially selected for the study. Thorough and relevant investigations were performed prior to inclusion. Those matching inclusion and exclusion criteria were admitted to the study. Other relevant physical features were also considered. A total of 180 patients, irrespective of sex, aged between 30 and 65 years were initially included from the out-patient department (OPD) of the same hospital. Thirty patients were excluded initially as they could not meet up the inclusion criteria, did not sign the consent form or some other reasons and did not start the treatment schedule. The remaining 150 patients were enrolled for the treatment after obtaining consent according to the World Health Organization (WHO)-Helsinki protocol.

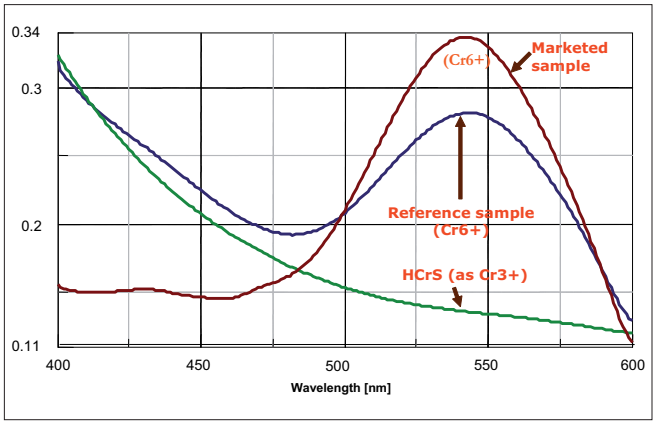

Figure 1: Comparative visible spectra of Cr (3+/6+) ions in different samples after treatment with oxidizing agents

Eligibility criteria

Eligibility was based on the inclusion criteria such as fasting blood glucose (FBG) level >120 mg/dl, post-prandial blood glucose (PPBG) level >180 mg/dl, change of work ability pattern, behavioral pattern, not received any antidiabetic drugs for more than 5 years and the willingness to participate in the trial with written consent. The exclusion criteria set for the present study were: any serious concomitant pathology of the liver, kidneys, heart, lungs or other organs; any subject under any treatment for systemic disorders and any subject receiving concomitant drug that may alter the study result.

Treatment schedule

One hundred fifty T2DM patients from OPD of J.B.Roy State Ayurvedic Medical College and Hospital, Kolkata, India, were enrolled. In this prospective, double-blind, placebo-controlled study, the patients were randomly divided into six groups, in a ratio of 2:1 (adjunct therapy versus placebo + OAD) by a random computer-generated number list. Capsules containing 10 mg of HCrS, which is equivalent to 200 µg of chromium plus excipients, were formulated into hard gelatin capsules. Labeled as 'drug-G', the capsules were identical with respect to size, shape, color (opaque white) and texture. The products were kept in the secure custody in the office of the Principal Investigator. Identical opaque white capsules were filled with only excipients (placebo referred to as 'drug-B'). The subjects were divided into six groups as follows:

- group I: glipizide + drug-G: 5 mg/day + 1 capsule BID (250 mg BID ≡ 200 µg Cr BID)
- group II: metformin + drug-G: 1 g/day + 1 capsule BID (250 mg BID ≡ 200 µg Cr BID)
- group III: pioglitazone+ drug-G: 30 mg/day + 1 capsule BID (250 mg BID ≡ 200 µg Cr BID)
- group IV: glipizide + drug-B: 5 mg/day + 1 capsule BID
- group V: metformin + drug-B: 1g/day + 1 capsule BID
- group VI: pioglitazone + drug-B: 30 mg/day + 1 capsule BID

All the patients in groups I through III were supplied with any one of the OAD and specific bottles of capsules (drug-G). Patients of groups IV–VI were supplied with any one of the OAD and specified bottles of capsules

(drug-B). One capsule was to be taken before lunch and the other was to be taken before dinner for a total duration of 2 months. Patients were given capsules and OAD for duration of 15 days at each visit and came for a total of four visits. Compliance was monitored by traditional pill-count method at each follow-up visit and at the end of the study. A schematic representation of the study design is given in Figure 2.

The diabetic symptoms were assessed by calculating the mean responses to a questionnaire that included the following items: polyurea, polydypsia, arthalgia, weakness, burning sensation and vertigo which are characteristic of diabetes. The subjects were asked to rate each item at the baseline and again during the 30 and 60 day visits based on a scale of 0–4 where '0' indicated no symptom, '1' occasional, '2' mild/poor, '3' moderate and '4' denoted severe. At the baseline and day 60 visits, subjects were advised to come after fasting overnight and with a sample of their first urine of the day collected in previously given sterilized container. Exactly 6–10 ml of blood was sampled and collected in vacutainer tubes between 9:00 AM and 11:00 AM on those days, to avoid diurnal variations and stored at 4°C until the assay. FBG, HbA_{1c}, LDL and CRP were measured. To estimate PPBG, blood was withdrawn from the patients 2 hours after 75 g glucose load in the same visit.

Statistical analysis

Percentage changes for measures were expressed as the difference between means of the baseline and final values divided by the mean of the baseline phase multiplied by 100. The difference in scores was calculated by subtracting values at baseline and 60 days for each variable respectively (including the subjective scores). These difference scores were then compared among groups using one-way analysis of variance (ANOVA) with *post hoc* pair wise comparisons of groups (groups I– VI) using the least significant difference (LSD) method. For all analyses, $P < 0.05$ was considered to be significant. Statistical analysis was performed using the computer statistical package SPSS/10.0 (SPSS, Chicago, IL, USA).

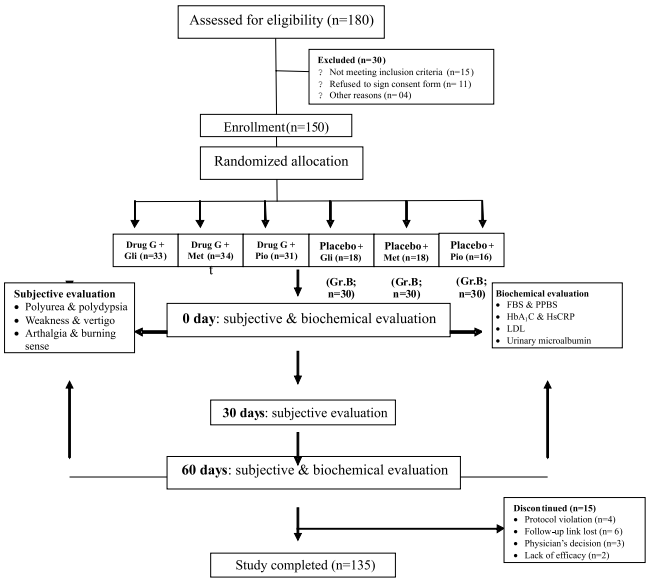

Figure 2: Schematics of study design

Results

Purity of herbo-chromium supplement

Purities of three batches of HCrS with respect to their components are given in Table 1. The table shows comparative values of the calculated amounts of the bioactives vis-à-vis experimentally determined amounts of the bioactives.

From the above result, it can also be seen that a consistent presence of chromium in the three batches of sample indicated reproducibility of the synthesis.

Proof of maintenance of Cr3+ oxidation state in herbo-chromium supplement under oxidizing circumstances

HCrS maintained its intrinsic chromium 3+ oxidation state under oxidizing conditions (ammonium persulfate) as opposed to a marketed chromium supplement which transformed into Cr6+ state [Figure 1]. Authentication of the method was performed using $CrCl_3.6H_2O$ as the reference sample, which also produced Cr6+ species after the oxidation.

A summary of the demographics is shown in Table 2. A total of 135 patients of T2DM completed the study. Thirty patients from each of the groups I, II and III (glipizide + drug-G, metformin + drug-G and pioglitazone + drug-G, respectively) completed the treatment schedule. Fifteen patients from each of the groups IV, V and VI (glipizide, metformin and pioglitazone with drug-B, respectively) completed the treatment schedule.

There were a total of 15 drop-out cases in this study, 8 of which from drug-G treated group (8.2%) and 7 from placebo treated groups (13.5%). The main reasons for study withdrawals were protocol violations, follow-up link lost or physician's decision, which may be due to lack of efficacy (mainly in the placebo treated groups). No treatment emergent adverse events were reported to the doctors by those who had completed the study. Overall improvement

Table 1: Content of different bioactives in three batches of HCrS

Batch no.	Amla fruit extract[a] (%w/w)		Processed Shilajit[b] (%w/w)		Chromium[c] (%w/w)	
	Calculated	Experimental	Calculated	Experimental	Calculated	Experimental
I	30	29.6	30	28.7	2	1.9
II	30	28.5	30	28.3	2	1.8
III	30	29.1	30	29.3	2	1.9

HCrS contains 10% w/w of $CrCl_3.6H_2O$ which is equivalent to 2% w/w of chromium [a]By HPLC-PDA; [b]by HPLC-PDA; [c]by AAS

Table 2: Demographic pattern of the patients who completed the study in its entirety

Characteristics	T2DM patients					
	Drug-G + Gli (n = 30)	Drug-G + Met (n = 30)	Drug-G + Pio (n = 30)	Placebo + Gli (n = 15)	Placebo + Met (n = 15)	Placebo + Pio (n = 15)
Age, mean (SD), years	49.2 (9.5)	48.8 (8.9)	50.4 (9.2)	47.2 (8.5)	47.9 (9.0)	51.4 (11.6)
Male:female	17:13	18:12	16:14	8:7	7:8	7:8
Weight, mean (SD), kg	58.2 (6.4)	61.4 (6.3)	60.8 (7.8)	60.9 (7.0)	59.9 (6.9)	59.1 (7.2)
Height, mean (SD), cm	160.5 (7.5)	161.7 (7.9)	158.8 (9.4)	157.4 (6.4)	156.8 (8.4)	157.2 (7.9)
Body mass index, mean (SD), kg/m^2	22.25 (3.3)	24.40 (2.9)	23.31 (5.8)	23.11 (2.5)	24.37 (3.3)	21.52 (4.0)

Gli, glipizide; Met, metformin; Pio, pioglitazone, drug-G, HCrS

in diabetic symptoms was observed in all the subjects, which was more pronounced in the drug-G treated groups, and this was quantified by subjective evaluations.

Subjective variables

The mean scores of the diabetic symptoms for each group at baseline and at 60 days were calculated [Tables 3A–C]. A decrease in a score was an indication of improvement. In the drug-G and OAD adjunct treated groups (groups I–III), the mean scores for all variables continuously decreased throughout the study, ranging from –47.4 to –59.4% (mean –51.9%), whereas the scores decreased slowly in the placebo plus OAD groups (groups IV–VI), ranging from –18.0 to –34.0% (mean –27.7%). The score differences between baseline and at day 60, in most of the variables, were statistically significant ($P \leq 0.045–0.001$) for all treated groups versus placebo (groups I versus IV, groups II versus V and groups III versus VI). These findings clearly indicated that administration of drug-G as an adjunct therapy had significant beneficial effects on T2DM patients when compared to that of only OAD treated groups.

Objective variables

Mean values (SD) of biochemical parameters for each treatment group at baseline and 60 days are summarized in Tables 4A–C.

Fasting blood glucose level

Patients receiving drug-G (groups I–III) as an adjunct therapy experienced a significant decrease in FBG (ranging from –12.4 to –16.6%; mean –14.6%), whereas less pronounced decrease in glucose level (ranging from –4.4 to –9.1%; mean –6.1%) was observed in patients receiving only OAD (groups IV–VI). The decrease of FBG was statistically significant ($P \leq 0.016–0.003$) for all treated groups versus respective OAD (groups I versus IV, groups II versus V and groups III versus VI) groups.

Post- prandial blood glucose level

A similar trend of decrease in PPBG (ranging from –12.4 to –16.3%; mean –14.2%) was observed after 2 months of treatment with drug-G along with OAD (groups I–III). The decrease in PPBG was less pronounced (ranging from –3.4 to –9.4%; mean –6.5%) in patients receiving only OAD (groups IV–VI). This improvement in control over PPBG was statistically significant ($P \leq 0.018–0.002$) for all treated groups versus respective OAD (groups I versus IV, groups II versus V and groups III versus VI) groups.

HbA_{1c} and HsCRP

T2DM patients who took drug-G as an adjunct therapy experienced a better decrease in HbA_{1c} (ranging from –5.2 to –6.7%; mean –6.1%) and HsCRP (ranging from –8.5 to –15.6%; mean –12.8.2%) levels compared to that of only OAD treated groups (ranging from –2.1 to –6.2%; mean –4.1% and –5.3 to –6.6%; mean –5.9%, respectively). However, these improvements were not statistically significant when compared between groups.

Table 3A: Mean (SD) values of objective variables at the baseline and on day 60 of treatment with drug-G with glipizide (group I; n = 30) and placebo with glipizide (group IV; n = 15) in T2DM patients

Parameters	Group I			Group IV			Group I versus group IV *P* values*
	Baseline	60 days	Δ%	Baseline	60 days	Δ%	
FBG (mg/dl)	136.8 (21.2)	116.6 (18.8)	−14.8	143.5 (27.1)	136.7 (29.4)	−4.7	0.003
PPBG (mg/dl)	265.5 (53.4)	222.4 (46.3)	−16.3	267.4 (58.6)	242.3 (55.5)	−9.4	0.018
HbA1c (%)	7.46 (1.07)	6.96 (0.98)	−6.7	7.45 (1.30)	7.29 (1.58)	−2.1	0.133
HsCRP (mg/dl)	6.14 (1.75)	5.18 (1.41)	−15.6	7.01 (1.81)	6.61 (1.63)	−5.7	0.057
LDL (mg/dl)	121.7 (32.0	113.4 (29.1)	−6.8	139.2 (28.5)	134.8 (22.7)	−3.2	0.443
Microalbumin (mg/dl)	18.3 (9.4)	14.6 (7.4)	−20.0	16.9 (9.7)	15.6 (7.8)	−7.8	0.023

**P* values were obtained by ANOVA followed by post hoc analysis for pair wise comparison between groups I and IV

Table 3B: Mean (SD) values of objective variables at the baseline and day 60 of the treatment with drug-G with metformin (group II; n = 30) and placebo with metformin (group V; n = 15) in T2DM patients

Parameters	Group II			Group V			Group II versus group V *P* values*
	Baseline	60 days	Δ%	Baseline	60 days	Δ%	
FBG (mg/dl)	141.7 (31.7)	124.1 (27.4)	−12.4	134.2 (13.5)	128.3 (13.3)	−4.4	0.009
PPBG (mg/dl)	261.7 (53.5)	229.3 (52.4)	−12.4	257.4 (36.1)	248.7 (37.1)	−3.4	0.002
HbA1c (%)	7.33 (1.10)	6.85 (0.96)	−6.5	7.79 (0.89)	7.31 (0.61)	−6.2	0.977
HsCRP (mg/dl)	5.5 (1.22)	5.02 (1.14)	−8.5	6.76 (1.55)	6.31 (1.38)	−6.6	0.945
LDL (mg/dl)	135.4 (29.5)	125.4 (20.7)	−7.4	139.1 (22.1)	133.9 (17.3)	−3.8	0.352
Microalbumin (mg/dl)	15.8 (8.4)	12.6 (7.0)	−20.8	13.8 (9.7)	12.5 (7.8)	−9.6	0.054

**P* values were obtained by ANOVA followed by post hoc analysis for pairwise comparison between groups II and V

Table 3C: Mean (SD) values of objective variables at the baseline and day 60 of the treatment with drug-G with pioglitazone (group III; n = 30) and placebo with pioglitazone (group VI; n = 15) in T2DM patients

Parameters	Group III			Group VI			Group III versus group VI *P* values*
	Baseline	60 days	Δ%	Baseline	60 days	Δ%	
FBG (mg/dl)	142.2 (20.0)	118.7 (23.3)	−16.6	139.4 (21.7)	126.7 (20.3)	−9.1	0.016
PPBG (mg/dl)	259.9 (48.7)	223.5 (46.1)	−14.0	259.3 (48.9)	242.0 (41.5)	−6.7	0.013
HbA1c (%)	7.51 (1.14)	7.12 (1.15)	−5.2	7.62 (0.79)	7.32 (1.10)	−3.9	0.682
HsCRP (mg/dl)	5.69 (1.50)	4.88 (1.32)	−14.2	6.01 (1.89)	5.69 (1.38)	−5.3	0.097
LDL (mg/dl)	128.5 (23.4)	121.0 (23.5)	−5.8	140.2 (14.4)	132.7 (13.1)	−5.3	0.995
Microalbumin (mg/dl)	16.3 (8.0)	12.7 (6.4)	−22.5	17.6 (9.2)	15.6 (7.7)	−11.6	0.111

**P* values were obtained by ANOVA followed by *post hoc* analysis for pair wise comparison between groups III and VI

Table 4A: Mean (SD) values of subjective variables at the baseline and day 60 of the treatment with drug-G with glipizide (group I; n = 30) and placebo with glipizide (group IV; n = 15) in T2DM patients

Parameters	Group I			Group IV			Group I versus group IV *P* values*
	Baseline	60 days	Δ%	Baseline	60 days	Δ%	
Polyurea	3.23 (0.77)	1.53 (0.68)	−52.6	2.67 (1.05)	1.93 (0.80)	−27.5	<0.001
Burning sensation	2.43 (0.97)	1.07 (0.58)	−56.2	2.33 (1.18)	1.73 (0.59)	−25.7	0.002
Weakness	3.17 (0.91)	1.60 (0.68)	−49.5	3.07 (0.70)	2.13 (0.64)	−30.4	0.016
Vertigo	2.40 (0.93)	1.17 (0.53)	−51.4	2.47 (0.74)	1.80 (0.41)	−27.0	0.022
Polydypsia	2.63 (0.89)	1.27 (0.69)	−51.9	2.47 (0.83)	1.73 (0.59)	−29.7	0.007
Arthalgia	2.57 (0.90)	1.30 (0.65)	−59.4	2.73 (0.88)	2.00 (0.66)	−26.8	0.033

Arbitrary scoring: 04 – severe; 03 – moderate; 02 – mild/poor; 01 – occasional and 00 – never; **P* values were obtained by ANOVA followed by post hoc analysis for pair wise comparison between groups I and IV

Table 4B: Mean (SD) values of subjective variables at the baseline and day 60 of the treatment with drug-G with metformin (group II; n = 30) and placebo with metformin (group V; n = 15) in T2DM patients

Parameters	Group II			Group V			Group II versus group V *P* values*
	Baseline	60 days	Δ%	Baseline	60 days	Δ%	
Polyurea	2.77 (0.94)	1.30 (0.75)	−53.0	2.93 (0.80)	2.20 (1.08)	−25.0	0.007
Burning sensation	2.47 (1.07)	1.27 (0.79)	−48.7	2.00 (0.93)	1.53 (0.83)	−23.3	0.003
Weakness	3.23 (0.73)	1.67 (0.61)	−48.5	3.00 (0.66)	2.20 (0.78)	−26.7	0.004
Vertigo	2.60 (0.93)	1.23 (0.63)	−52.6	2.40 (1.12)	1.80 (0.86)	−25.0	0.002
Polydypsia	2.70 (1.02)	1.30 (0.70)	−51.9	2.60 (0.63)	2.13 (0.74)	−18.0	<0.001
Arthalgia	2.60 (1.04)	1.37 (0.81)	−47.4	2.27 (1.03)	1.73 (0.80)	−23.5	0.005

Arbitrary scoring: 04 – severe; 03 – moderate; 02 – mild/poor; 01 – occasional and 00 – never; **P* values were obtained by ANOVA followed by post hoc analysis for pair wise comparison between groups II and V

Table 4C: Mean (SD) values of subjective variables at the baseline and day 60 of the treatment with drug-G with pioglitazone (group III; n = 30) and placebo with pioglitazone (group VI; n = 15) in T2DM patients

Parameters	Group III			Group VI			Group III versus group VI *P* values*
	Baseline	60 days	Δ%	Baseline	60 days	Δ%	
Polyurea	3.00 (0.91)	1.43 (0.73)	−52.2	3.20 (0.78)	2.27 (0.59)	−29.2	0.019
Burning sensation	2.47 (1.01)	1.13 (0.57)	−54.1	2.53 (1.00)	1.73 (0.59)	−31.6	0.030
Weakness	3.00 (0.83)	1.57 (0.50)	−47.8	3.13 (0.92)	2.07 (0.59)	−34.0	0.159
Vertigo	2.67 (0.84)	1.30 (0.65)	−51.3	2.40 (1.12)	1.60 (0.74)	−33.3	0.022
Polydypsia	2.67 (0.96)	1.20 (0.61)	−55.0	2.87 (0.92)	2.00 (0.66)	−30.2	0.011
Arthalgia	2.57 (0.97)	1.20 (0.61)	−53.3	2.80 (1.01)	1.93 (0.70)	−31.0	0.045

Arbitrary scoring: 04 – severe; 03 – moderate; 02 – mild/poor; 01 – occasional and 00 – never; **P* values were obtained by ANOVA followed by post hoc analysis for pair wise comparison between groups III and VI

Urinary micro albumin level

A trend of decrease in urinary microalbumin level (ranging from –20.0 to –22.5%; mean –21.1%) was observed after 2 months of treatment with drug-G along with OAD (groups I–III) which was less pronounced (ranging from –7.8 to –11.6%; mean –9.7%) in patients receiving only OAD (groups IV–VI). This improvement was statistically significant when compared between groups I and IV ($P < 0.023$) and groups II and V ($P < 0.05$).

Serum low density lipoprotein level

Patients receiving drug-G (groups I–III) showed 6–7% decrease in serum LDL level which was marginally better than that of only OAD treated groups (3–5%), but was not statistically significant however.

Discussion

Diabetes pervasively affects the global population and it spreads in every stage of life, starting from infancy, youth, middle age and senescence. T2DM is the major driver of the epidemic, which accounts for more than 90% of all diabetes cases.[16] Several OAD are currently available to control T2DM but these drugs too suffer from a number of drawbacks such as, hypoglycemia, nausea, abnormal liver function, diarrhea, lactic acidosis, drug interaction that impairs their total acceptance.[17] Apart from the adverse side effects of OAD, development of drug resistance is another common deficiency which requires increasing doses of OAD and/or addition of new group(s) of OAD with the progression of the disease. Dietary supplements, including antioxidants, extracts of medicinal plants and essential mineral supplementation along with OAD may attenuate the existing deficiencies of management and treatment of T2DM.

Several clinical studies have suggested that chromium supplementation provides a better option for the management of T2DM or in persons at high risk of T2DM.[18] But most of the clinical reports do not provide a quantitative overview; some of the studies were uncontrolled or observational studies that were unable to demonstrate the intrinsic effect of chromium supplementation. Based on the existing study reports and literature review it is difficult to assess the contribution of chromium.[8] One of the probable reasons of such inconsistencies regarding the

beneficial effect of the chromium supplement could be its facile conversion from Cr (III) to Cr (VI) during the formation of, e.g., niacin- and picoline-bound trivalent chromium complex[19] with their facile oxidation during the systemic passage. Considering the importance of the ligand, which is largely associated with the maintenance of the oxidation status of trivalent chromium in the supplement, a product was developed involving a polyphenolic antioxidant-chromium complex, where trivalent chromium remains unchanged even in the presence of an oxidative environment.[20]

The present finding further suggests that adjunct therapy of HCrS (drug-G) could attenuate T2DM complications. This is reflected by the significant lowering of FBG, PPBG and a decreasing trend in HbA_{1c}, HsCRP, LDL and urinary microalbumin levels of the treated subjects. This observation is supported by the distinct improvement in characteristic diabetic symptoms, viz., polyurea, polydypsia, arthalgia, weakness, burning sensation and vertigo. The patients receiving only OAD also showed improvement in the above mentioned characteristic symptoms, but to a comparatively lesser extent. The two major symptoms of diabetes, viz., polyurea and polydypsia, which are directly related to hyperglycemia, significantly decreased after 60 days of administration of drug-G with OAD patients compared to those of the placebo treated groups. The decrease in HbA_{1c} level was not statistically significant in patients subjected to drug as an adjunct therapy. This is reasonably explained by the short period of the treatment. Simultaneous decrease in symptoms like weakness, which is related to glycation of hemoglobin, indicated that prolonged use of drug-G may elicit better response.

Insulin resistance, the major contributing factor of T2DM, is associated with significant increase in the risk factor of atherothrombic disease. Apart from the dysfunction of coagulation and fibrinolysis process, dyslipidemia and endothelial dysfunction are the key factors for the development of atherothrombic disease.[21] In this study, HsCRP level was estimated to assess the state of subclinical systemic inflammation that occurred mainly due to endothelial dysfunction.[22] The decrease in HsCRP level distinctly manifested in adjunct therapy with drug-G, compared to that of placebo with OAD. This finding indicated beneficial interaction of chromium at insulin-receptor site resulting in the decrease in insulin resistance and hyperglycemia.[23] Significant decrease in symptoms like arthalgia supported the above findings. Although the proof of efficient delivery of chromium at the receptor site would need further study, a circumstantial evidence was obtained. Insulin resistance directly affects the macrovascular structure leading to loss of albumin through urine. Perceptible decrease in urinary microalbumin level in adjunct therapy with drug-G compared to that with only OAD treatment indicated increase in insulin sensitivity in the title group (HCrS). Significant decrease in symptoms like burning sensation also supported the above findings. Thus, a favorable glycemic control in T2DM was observed when OADs were administered along with the HCrS, in comparison to the OAD group. As T2DM is a multisystem disorder, different types of subjective features were observed which were also appreciably controlled by coadministration of drug-G with OAD. The observed decrease in hyperglycemia with concomitant decrease in diabetic symptoms indicates that drug-G could be a useful candidate for the treatment, as an adjunct therapy of T2DM subjects.

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