Original Article

Evaluation Series on Safety and Efficacy of Nutritional Supplements in Newly Diagnosed Hyperglycemia: A Placebo-Controlled, Randomized Study

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Abstract

Background: Diabetes is endemic with developing economies contributing to the bulk of this pandemic. Despite the evidence of incremental benefit of glycemic control starting early in life, acceptance of and adherence to modern medications remain suboptimal. **Aims:** To determine the hemoglobin A1c (HbA1c)-lowering efficacy and safety of nutritional supplement, PreCrea®, in adult Indians with newly diagnosed hyperglycemia. **Materials and Methods:** Double-blind, randomized study conducted in six diabetes centers in India. A total of 193 treatment-naïve subjects with newly diagnosed hyperglycemia and fasting plasma glucose (FPG) >100 mg/dL were randomized into either PreCrea® 600 mg (n = 90) or matched placebo (n = 89) capsules twice daily, along with lifestyle modification, for 12 weeks. The main outcomes were changes in HbA1c and FPG levels, attainment of the American Diabetes Association (ADA)-defined goals for HbA1c, and clinical and biochemical measures of safety. **Results:** At 12 weeks, mean HbA1c in PreCrea® group reduced by 0.91% compared with 0.08% increase in the placebo group (P < .001). The reductions in the mean FPG at week 4 (P < .001) and week 12 (P = 0.04) were significant compared to the baseline. ADA goal of HbA1c <7% increased from 15.5% at the baseline to 35.6% at week 12 in PreCrea® subjects. Clinical safety and biochemical safety did not change. Hypoglycemia and weight gain were not observed with PreCrea®. **Conclusions:** Nearly 1% point reduction in HbA1c at week 12 with PreCrea® is comparable with most first-line glucose-lowering drugs. The safety and tolerability of PreCrea® highlights its potential as a first-line therapy in newly detected hyperglycemia.

Keywords: American Association of Clinical Endocrinologists (AACE) guidelines, alternate medicine, complementary medicine, dietary supplement, HbA1c-lowering, newly diagnosed hyperglycemia, nutritional supplement, prediabetes, primary prevention diabetes

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Introduction

Increasing upward mobility compounded with genetic predisposition has resulted in an incremental prevalence of diabetes and prediabetes starting at a younger age among people in emerging economies such as India,

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China, and several Southeast Asian, African, and Latin American countries. Complications including myocardial infarction develop aggressively in young diabetes patients. The United Kingdom Prospective Diabetes Study (UKPDS) showed that early glucose-lowering therapy for young adults with newly diagnosed Type 2 diabetes was associated with a decreased risk of microvascular complications, myocardial infarction, and death from any cause.[1] Therefore, it is critical to have treatment options for young adults with newly diagnosed hyperglycemia that optimize diabetes control and reduce complications.

Despite the availability of various guidelines and new pharmacotherapies globally, the management of patients with prediabetes and diabetes remains less than satisfactory. Lifestyle changes, including regular exercise and diet, are essential and the 2015 diabetes management algorithm by the American Association of Clinical Endocrinologists (AACE) proposes metformin plus lifestyle modification as the first line of therapy in newly diagnosed diabetes patients with an entry glycosylated hemoglobin [hemoglobin A1c (HbA1c)] level of <7.5%.[2] However, maintaining an adequate and consistent lifestyle is not achievable in a majority of the patients. Additionally, metformin, while being effective, has gastrointestinal side effects in nearly 30% of the patients[3] and other available pharmacological options are associated with side effects and classwide-effect safety warnings. Achieving glycemic control in patients with Type 1 or Type 2 diabetes mainly depends on the patient's adherence to the treatment plan. Nonadherence to metformin, resulting in primary treatment failure, has been reported in approximately 39.7% of the patients.[4] Concern of adverse effects and inherent psychological barriers against being on a "drug for life" are among the major reasons for low adherence. Therefore, efforts should be directed to individualize therapy based on ethnic/cultural beliefs and traditions. The 2015 position statement by AACE calls for an HbA1c target of ≤6.5% (in patients with no risk of hypoglycemia and no concurrent serious illness), which should be optimally achieved in a safe manner without the risk of hypoglycemia and weight gain.[2]

Availability of a food-derived formulation that could safely and effectively lower HbA1c could be culturally more acceptable because of being perceived as a "softer" therapeutic option and therefore, could lead to significant public health benefits. However, while there are many dietary supplements, which claim glucose-lowering efficacy, none are backed with the rigor of randomized, double-blind clinical trial evidence. The aim of this study, therefore, was to evaluate the glucose-lowering efficacy and safety of PreCrea®, a proprietary nutritional supplement in patients with newly diagnosed hyperglycemia in India, where diabetes is endemic. PreCrea® contains Ivy gourd fruit extract (*Coccinia cordifolia* or *Coccinia indica)* powder, *Gymnema sylvestre* leaf extract powder, fenugreek (*Trigonella foenum-graecum*), chromium picolinate, and biotin [Table 1]. PreCrea® is available in many countries including the USA. The study was performed as part of the evaluation series on safety and efficacy of nutritional supplements (ESSENS),[5] which aims to critically evaluate the efficacy of nutritional supplements and includes further evaluation of longer term adoption and adherence rates and clinical outcomes as compared to prescription drugs.

Materials and Methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled study conducted at six primary care diabetes centers across India (Total Diabetes Hormone Institute, Indore, Madhya Pradesh, India; DiaCare — Diabetes Care and Hormone Clinics 1 and 2, Ahmedabad, Gujarat, India; Diabetes Care Centre, Jaipur, Rajasthan, India; Bhatia Hospital, Mumbai, Maharashtra, India; Inamdar Multispecialty Hospital, Pune, Maharashtra, India; St. Johns Medical College, Department of Endocrinology, Bangalore, Karnataka, India). The study was approved by the local institutional review board and an independent ethics committee at each participating site. Written informed consent was obtained from each participant prior to enrolment in the study. The study was conducted from Jan 25, 2014 to Oct 31, 2014.

Study participants

Treatment-naïve newly diagnosed hyperglycemia subjects aged 18-65 years with fasting plasma glucose (FPG) >100 mg/dL were eligible to participate in the study. Individuals with Type 1 diabetes mellitus, on insulin or any other oral antidiabetic therapy, having known cardiovascular disease, uncontrolled blood pressure, impaired renal function, clinically significant peripheral edema, impaired hepatic or renal function, with active liver disease, ongoing steroid therapy, malignancy, known hypersensitivity to study drugs, or history of alcohol abuse or mental disorder were excluded. Pregnant and lactating women were also excluded.

In addition, randomizing a small group of "on metformin" patients in a separate arm of the study was planned. However, this step was discontinued later because of logistic reasons and also because this was not the primary objective of the study.

Table 1: PreCrea® and placebo composition details

Criteria	Details
Scientific name The Latin binomial name and common name	A combination blend of food-derived ingredients: Ivy gourd fruit extract powder (*Coccinia cordifolia*) *Gymnema sylvestre* leaf extract powder Fenugreek seed extract powder (*Trigonella foenum-graecum)* Black pepper seed extract powder (*Piper nigrum*) Chromium picolinate Biotin
Brand name and manufacturer The proprietary product name (i.e., brand name) and the name of the manufacturer	PreCrea® Manufacturer: PreEmptive Meds, Inc., USA
Ingredient extraction/manufacturing The part(s) of plant used to produce the product or extract and solvent used	Ivy gourd fruit extract powder (*Water-based solvent*) *Gymnema sylvestre* leaf extract powder (*Water-based solvent*) Fenugreek seed extract powder (*Water-based solvent*) Black pepper seed extract powder (*Water-based solvent*) Chromium picolinate Biotin
Serving size The dosage of the product, the duration of administration, and how these were determined	600 mg twice a day in double zero size hydroxypropyl methylcellulose (HPMC) opaque yellow capsules (vegetarian, kosher, and halal certified) Duration: 90 days for the trial period How dosage and duration is determined: Twice daily dosage (one capsule in the morning and one at night) was based on the half-life of food-based ingredients, quantity of standardized actives in each ingredient, and proprietary knowledge gained from US clinical experience of 8 years among thousands of existing consumers
Dosage The content (e.g., weight, concentration may be given in ranges where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form. Added materials, such as binders, fillers, and other excipients (e.g., 17% maltodextrin, 3% silicon dioxide per capsule) should also be listed)	Ivy gourd fruit extract powder: 300 mg *Gymnema sylvestre* leaf extract powder: 150 mg Fenugreek seed extract powder: 30 mg Black pepper seed extract powder: 15 mg Chromium picolinate: 17 mcg Biotin: 1 mcg Excipients (starch, magnesium stearate) 100 mg
Placebo The rationale for the type of control or placebo used	As the study was double-blinded, the placebo capsule used was double zero HPMC opaque yellow capsule and filled with 600 mg of maize starch
Practitioners A description of the practitioners (e.g., training and practice experience) who are a part of the intervention	Allopathy-trained endocrinologists and internal medicine doctors practicing primary prevention in an outpatient setting

Study procedures

All subjects underwent the screening procedures including those for determining significant medical history, clinical evaluations (vital signs and physical examination), 12-lead electrocardiogram, routine microscopic urine examination, and biochemical investigations [complete blood count; FPG and HbA1c, triglycerides (TGs); renal function tests {blood urea nitrogen (BUN); total bilirubin; serum creatinine); and liver function tests (alanine transaminase (ALT); aspartate transaminase (AST); alkaline phosphatase (ALP)] at baseline. All laboratory investigations were performed at a centralized facility.[6]

Eligible subjects were assigned a unique subject number at baseline. Each eligible subject received one sealed envelope containing information on the subject number in the front and bottle number on the inner side of the envelope. The subjects were randomly assigned in a 1:1 ratio using these sealed envelopes to receive either PreCrea® 600 mg capsule twice daily or a matching placebo for 12 weeks in a double-blinded manner. All subjects were also advised lifestyle modifications including standardized diet and exercise.

At week 4 and week 12 (±4 days) of the study treatment, the subjects visited the trial site for clinical evaluation and laboratory assessments (FPG at week 4 and week 12; HbA1c, TG, ALT, AST, ALP, serum creatinine, total bilirubin, and BUN levels at week 12).

Safety assessments performed during the entire course of the study included clinical examination, vital signs recording, adverse event (AE) monitoring, and concomitant medication assessment. Compliance was computed through drug accountability records (number of used and unused capsules) and verbal confirmation from the subjects at each study visit before dispensing the study medication for the remaining period.

Outcome measures

Primary efficacy outcome measures were changes in HbA1c levels from the baseline at week 12 (absolute and percent). Additional outcome measures were the percentage of patients achieving HbA1c levels of less than 7% at week 12, absolute and percent change from the baseline in FPG at weeks 4 and 12, and in TG at week 12. The primary safety measures were changes in renal and liver function parameters at week 12. The tolerability to PreCrea® and incidences and severity of AEs were also recorded. Additional analysis was performed to determine the statistical significance of shift in HbA1c levels from the baseline.

Statistical study

Assuming the rate of subjects achieving normal blood glucose level to be around 30%, a sample size of approximately 210 participants was decided in order to detect an odds ratio of at least 1.5 with a power of 80% and an alpha risk of 5% for a criterion positive for at least 15% of the subjects in the population defined by the nature of the disease. However, considering a 10% dropout, 200 subjects were planned to be enrolled. All categorical variables are expressed as the means of frequency counts and percentages. All continuous variables are summarized as number, mean, and standard deviation (SD). Baseline parameters in the two groups were compared using two sample *t*-test at each post baseline visit. Similarly, paired *t*-test was applied to compare the baseline data with each postbaseline visit data in each treatment group separately. Statistical significance was assessed at 5% ($\alpha = 0.05$) level of significance. For primary efficacy outcome measures, univariate analysis (analysis of variance for quantitative variables; chi-square or Fisher's exact test for nonordered qualitative variables, and Kuskal–Wallis test for ordered qualitative variables) were performed. Bowker test (test for marginal homogeneity) was used to determine the significance of shift in HbA1C from the baseline to week 12.

Results

Baseline data

A total of 285 subjects were screened, out of which 238 subjects satisfied all the eligibility criteria. Three subjects with FPG <100 mg/dL were enrolled with waivers. Of these, 193 treatment-naïve subjects were randomized to receive either PreCrea® ($n = 97$) or placebo ($n = 96$). A total of 90 subjects in the PreCrea® group and 89 subjects in the placebo group completed the study and were included in the final analysis [Figure 1].

The mean age of the subjects was 51.2 ± 8.25 years in the PreCrea® group versus 51.7 ± 8.07 years in the placebo group, and 51.4% (92 of 179 subjects) were males. All subjects were Indian. Although the mean body weight and BUN levels were slightly higher in the placebo group (71.8 ± 12.2 kg vs 67.2 ± 12.3 kg; 11.9 ± 3.63 mg/dL vs 10.8 ± 3.19 mg/dL), there were no other significant difference between the two groups at the baseline [Table 2].

Primary outcomes

Treatment with PreCrea® resulted in a significant reduction in mean HbA1c from 8.3 ± 1% (67 mmol/mol) at the baseline to 7.4 ± 1% (57 mmol/mol) at week 12 ($P < .001$) [Table 3]. The absolute reduction in HbA1c levels was 0.91 % in the PreCrea® group versus 0.08% in the placebo group. The percent reduction in HbA1c with PreCrea® (10.17%) was significantly greater compared to the placebo ($P < .001$).

Additional outcomes measures

Significant reductions in mean FPG levels were observed within the PreCrea® (159.3 ± 57.43 mg/dL to

Table 2: Baseline clinical and biochemical characteristics of the study population

Parameters	PreCrea® *N* = 90	Placebo *N* = 89	*P* value
Number of females, *n* (%)	49 (54.4%)	37 (41.5%)	.10
Number of males, *n* (%)	41 (45.6%)	52 (57.8%)	
Age (Years)	51.2±8.25	51.7±8.07	.68
Body mass index (kg/cm^2)	25.7±4.3	26.6±4.1	.15
Height (m)	1.61±0.17	1.64±0.08	.13
Weight (kg)	67.2±12.3	71.8±12.2	.01
Alanine transaminase (U/L)	43.7±13.87	47.2±16.17	.12
Aspartate transaminase (U/L)	23.1±9.10	24.6±10.88	.33
Alkaline phosphatase (U/L)	97.6±29.44	91.6±22.88	.13
Blood Urea Nitrogen (mg/dL)	10.8±3.19	11.9±3.63	.04
Glycosylated hemoglobin HbA1C (%, mmol/mol)	8.3±1.0 (67)	8.0±0.8 (64)	.14
Fasting plasma glucose (mg/dL)	159.3±57.43	163.7±51.08	.59
Total bilirubin (mg/dL)	0.48±0.19	0.54±0.25	.07
Serum creatinine (mg/dL)	0.86±0.19	0.91±0.21	.13
Triglycerides (mg/dL)	148.2±71.47	169.7±91.18	.08

SI conversion factors: Blood urea nitrogen (mg/dL) × 0.714 to obtain blood urea nitrogen (mmol/L), Bilirubin (mg/dL) × 17.104 to obtain bilirubin (μmol/L), creatinine (mg/dL) × 88.4 to obtain creatinine (μmol/L), triglyceride (mg/dL) × 0.0113 to obtain triglyceride (mmol/L), HbA1c(%) × 10.93-23.5 to obtain HbA1c (mmol/mol), Fasting plasma glucose (mg/dL) × 0.0555 to obtain fasting plasma glucose (mmol/mol)

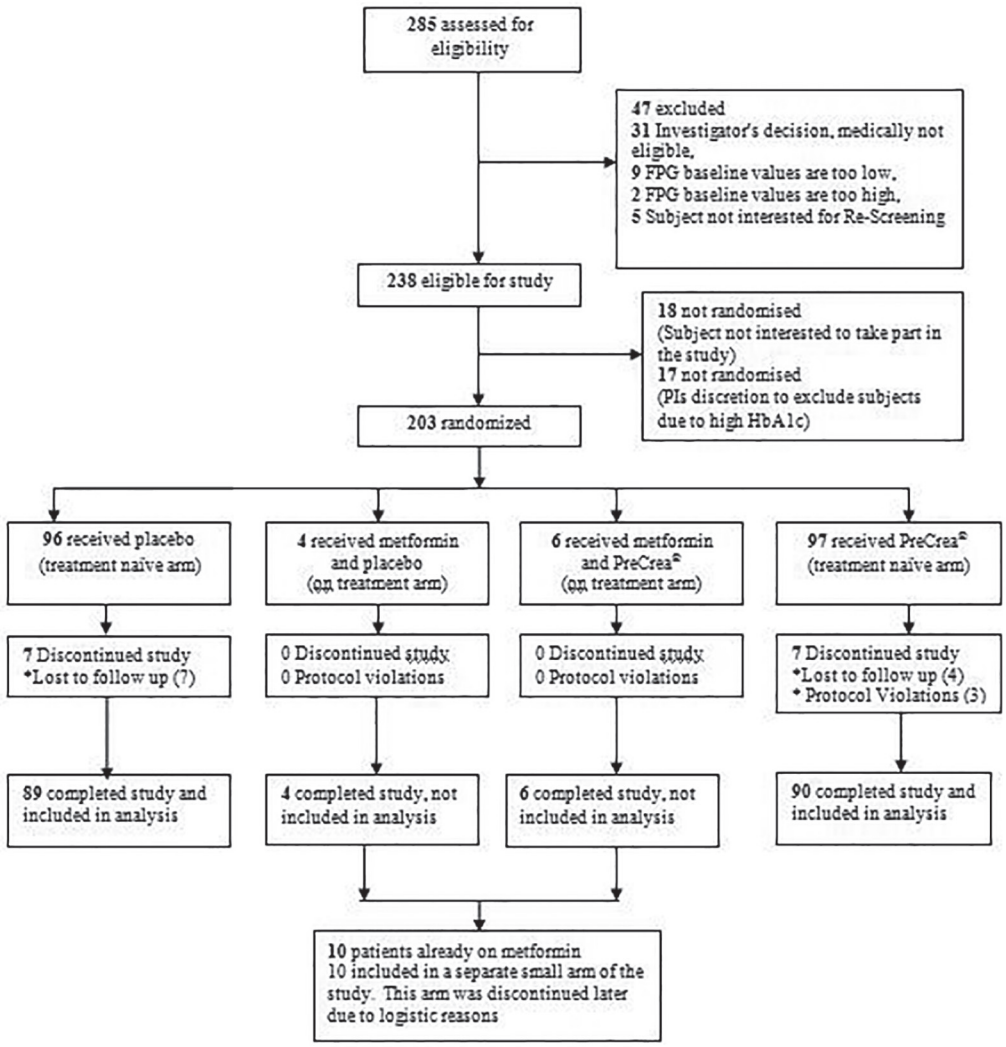

Figure 1: CONSORT flow diagram
This is a flow diagram of the progress of each treatment arm through the phases of randomized trial such as enrolment, intervention allocation, and data analysis

134.4 ± 40.21 mg/dL; −8.275%; $P < .001$) and placebo (163.7 ± 51.08 mg/dL to 151.5 ± 45.64 mg/dL; −2.073%; $P = .04$) groups at week 4 as compared to the baseline. However, at week 12, reduction in FPG was significant only for the PreCrea® group (159.3 ± 57.43 mg/dL to 145.1 ± 49.72 mg/dL; −1.829%, $P = .04$) [Table 3]. The reductions in FPG were not statistically significant between the treatment groups ($P = .35$). Treatment with PreCrea® also resulted in significant reductions in mean serum TG at week 12 (148.2 ± 71.47 mg/dL to 131.8 ± 66.76 mg/dL; −4.222%; $P = .02$); however, the reduction was not significant in the placebo group ($P = .45$). Reduction in serum triglyceride was not statistically significant between the treatment groups ($P = .43$) [Table 3].

Treatment with PreCrea® for 12 weeks resulted in a significant increase (shift) in the number of patients with HbA1c < 7% by 20.1% while the number of patients with HbA1c >9% decreased by 17.8% ($P < .001$). The shift in HbA1c was not significant in the placebo group ($P = .50$) [Figure 2].

The shift analysis of HbA1c data was also performed by categorizing patients into four tiers (HbA1c <7%, 7-7.9%, 8-8.9%, and ≥9%). At week 12, the PreCrea® group demonstrated steady improvement with mean actual decrease in HbA1c levels by −0.21%, −0.57%, −0.93%, and −1.71% in HbA1c tiers <7%, 7–7.9%, 8–8.9%, and ≥9%, respectively. In the placebo group, mean HbA1c levels increased by 0.31% and 0.33% in HbA1c tiers <7% and 7–7.9%, respectively, whereas it decreased by −0.23% and −0.32% in HbA1c tiers 8-8.9% and ≥9% at week 12 [Figure 3].

Primary safety outcome and tolerability

Results of the laboratory tests show that PreCrea® may be safe with respect to hepatic and renal markers.

Table 3: Treatment effect on efficacy and safety measures

Parameter	PreCrea® (*n* = 90)			Placebo (*n* = 89)			*P* value†
	Baseline	12 weeks	*P* value*	Baseline	12 weeks	*P* value*	
Efficacy parameters							
Glycosylated hemoglobin, % (mmol/mol)	8.3±1.0 (67)	7.4±1.0 (57)	<.001	8.0 ±0.8 (64)	8.1 ±1.4 (65)	.49	<.001
Fasting plasma glucose, mg/dL	159.3±57.43	145.1±49.72	0.04	163.7±51.08	158.4±58.43	.43	.35
Serum triglycerides, mg/dL	148.2±71.47	131.8±66.76	0.02	169.7±91.18	162.9±90.59	.45	.43
Safety parameters							
Blood urea nitrogen, mg/dL	10.8±3.19	10.8±3.43	0.88	11.9±3.63	11.6±3.56	.51	.73
Serum creatinine, mg/dL	0.86±0.19	0.91±0.23	0.01	0.91±0.21	0.93±0.23	.37	.56
Total bilirubin, mg/dL	0.48±0.185	0.49±0.2	0.60	0.54±0.254	0.53±0.26	.83	.62
Alanine transaminase, U/L	43.7±13.87	44.4±15.16	0.66	47.2±16.17	46.4±18.44	.99	.80
Alkaline phosphatase, U/L	97.6±29.44	98.6±25.51	0.21	91.6±22.88	94.3±20.7	.12	.98
Aspartate aminotransferase, U/L	23.1±9.1	23.2±10.38	0.93	24.6±10.88	23.6±10.97	.87	.85

All values are mean ± standard deviation, SI conversion factors: HbA1c(%) × 10.93-23.5 to obtain HbA1c (mmol/mol), Fasting plasma glucose — multiply by 0.0555 to convert to mmol/mol, triglycerides, multiply by 0.0113 to convert to mmol/L, for blood urea nitrogen in mmol/L multiply by 0.714, for creatinine in µmol/L multiply by 88.4, for bilirubin in µmol/L multiply by 17.104, **P* value compared to the baseline, †*P* = .001 compared to the baseline.

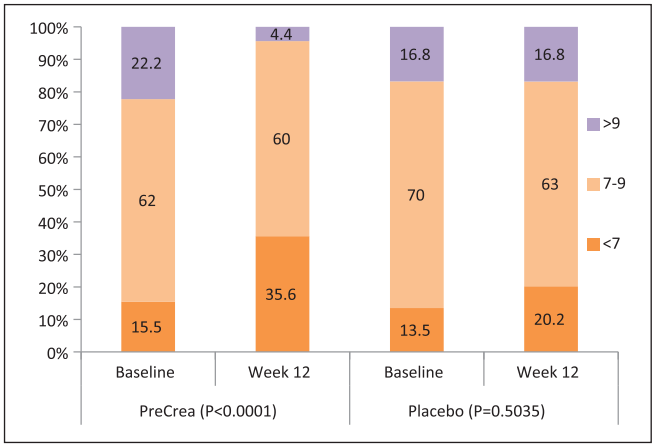

Figure 2: Shift in percentage of patients in HbA1c <7%, 7-9%, and >9% tiers

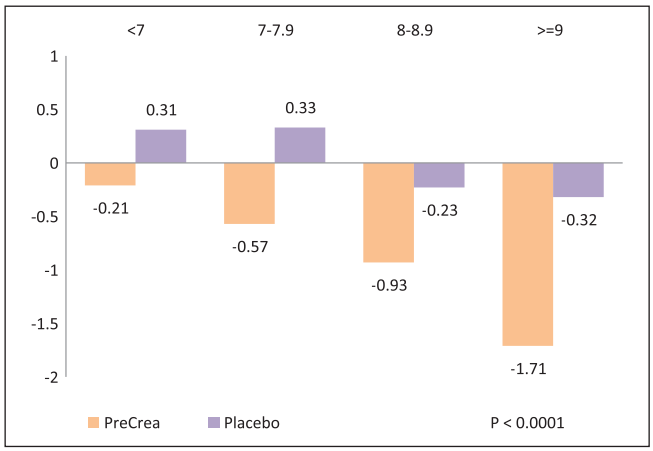

Figure 3: Shift in percentage of patients in HbA1c <7%, 7-7.9%, 8-8.9%, and ≥9% tiers

Mean percentage change from the baseline in safety parameters including AST (*P* = .85), ALT (*P* = .80), ALP (*P* = .98), serum creatinine (*P* = .56), BUN (*P* = .73), and total bilirubin (*P* = .62) was comparable between the two groups [Table 2].

PreCrea® was well-tolerated for 12 weeks and none of the patients discontinued treatment during the study. All AEs were transient and none were severe. A total of 42 AEs (25 in the placebo group and 17 in the PreCrea® group) were reported wherein 41 were mild and only one AE was moderate in severity. In the PreCrea® group, 16 (17.8%) patients experienced mild AEs and 1 (1.1%) experienced a moderate AE. However, total reports of AEs were more for the placebo group (28.1%) as compared with the PreCrea® (18.9%) group. The frequently reported AEs were hypertriglyceridemia, fatigue, elevated eosinophil counts, elevated HbA1c level, common cold, and urinary tract infection.

There was no clinically relevant change in any of the laboratory safety parameters at the end of the study [Table 2].

The percent change in body weight from the baseline in both the groups was comparable at week 4 (PreCrea® 0.226% vs placebo −0.264%; *P* = .09) and week 12 (PreCrea® 0.291% vs placebo −0.342%; *P* = .36). Hypoglycemia is defined as FPG ≤70 mg/dL by the American Diabetes Association (ADA).[7] There were no patient-reported event of hypoglycemia during the study duration. PreCrea® treatment did not produce any drastic change in complete blood count. No significant change in the vital signs was observed.

This study evaluated the glucose-lowering efficacy and short-term safety profile of PreCrea® in a primary prevention setting in India. A 12-week treatment with PreCrea® resulted in nearly 1% point reduction in HbA1c levels. Additionally, no safety concern was encountered with PreCrea® during the 12-week treatment period.

Discussion

Glucose-lowering efficacy and the mechanisms of action of PreCrea®

PreCrea® consists of a mixture of food-derived bioactive ingredients [Table 1] with distinct pharmacological activity or activities and the ingredients can be standardized for predictable results. The qualitative and quantitative rationales for combining the specific ingredients in double zero vegetarian capsules with twice daily dosing is proprietary to the investigational product, PreCrea®. The use of each ingredient in the combination is based on complementary and synergistic mechanisms of action in glucose metabolism and inflammatory pathways, bioavailability, and importantly, stability in harsh weather conditions, which is common to low-income countries of the world.

Ivy gourd fruit extract powder contains several triterpenoid saponins, some of which are natural inhibitors of glucose-6-phosphatase, the enzyme responsible for gluconeogenesis and glycogenolysis.[8] Gymnemic acid, active ingredient in *Gymnema sylvestre* leaf, is structurally similar to glucose. These molecules fill the receptor locations on the taste buds and on the absorptive intestinal layers, thereby preventing its activation by sugar molecules in food and eventually curbing sugar craving and preventing sugar molecule absorption by the intestine.[9,10] The soluble dietary fibers of fenugreek seeds act *via* the inhibition of carbohydrate digestion and absorption, and enhancement of peripheral insulin action.[11] Chromium picolinate, and biotin are known antioxidants and enhance insulin sensitivity.[12,13]

For use of any food-derived formulation as a pharmacotherapy, the final preparation needs to be tested independently for its efficacy and safety because of unknown interactions among different ingredients. In our study, a short-term treatment with PreCrea® demonstrated not only hypoglycemic efficacy but also considerably reduced serum triglyceride levels. This indicates a possible synergistic action between the ingredients of PreCrea®. More importantly, despite a substantial HbA1c-lowering effect, PreCrea® was not associated with any AE of hypoglycemia or weight gain.

Clinical relevance of the findings

Lowering of HbA1c to 7% or below (ADA glycemic target for HbA1c) reduces/delays the development of microvascular complications and if implemented soon after the detection of hyperglycemia, is associated with long-term reduction in the number and intensity of microvascular diseases.[14] Studies in various Western countries have shown that the prevalence of inadequate glycemic control (HbA1c > 7%) in the United Kingdom is 76% and in the United States is 50%.[15] Diabetes management goals set by the Brazilian Diabetes Society are achieved in 46% of the patients with respect to HbA1c levels and in 24% with respect to the body mass index.[16] On the other hand, in a cross-sectional study from 12 countries in Asia, 54% of those surveyed did not have a recorded value of HbA1c. The study measured HbA1c independently, and 55% were found to have values higher than 8%.[17] Studies in Thailand[18] and Pakistan[19] reported that only 26.3% and 31.4% of the patients showed HbA1c < 7%, respectively. The limited studies available on diabetes care in India indicate that 50 to 60% of patients with Type 1 or Type 2 diabetes do not achieve their glycemic target.[20]

In our study, approximately 35.6% of the patients in the PreCrea® group achieved their glycemic target with 12 weeks of treatment. The percentage of patients with HbA1c > 9% in the PreCrea® group decreased significantly from 22.2% to 4.4% at the end of week 12.

The current guidelines from the ADA and AACE recommend early initiation of metformin as a first-line drug for monotherapy and in combination therapy. However, gastrointestinal intolerance occurs frequently with metformin. These effects subside once the dose is reduced or when administered with meals but 5% of the patients do not tolerate even the lowest dose of metformin.[21] Hypoglycemia and weight gain are the most common side effects of other second-line agents such as sulfonylureas and meglitinides, whereas body fat gain, fluid accumulation, bone fractures, and increased risk of bladder cancer are the most common side effects of glitazones.[7] Sodium glucose cotransporter 2 inhibitors have been associated with an increased incidence of genital and urinary tract infections.[22] We also know from clinical experience that younger, newly diagnosed patients deal with the shock factor of learning of their dysglycemia with denial and are reticent to start prescription drugs. Under these circumstances, the availability of a food-based, efficacious, and safe therapeutic solution that appeals to the social and cultural sensibilities of the people from countries such as India, where traditional medicine systems coexist, could be very beneficial.

The cost factor

In the emerging markets, choosing an antidiabetic therapy is largely influenced by the cost of the therapy rather than its overall efficacy and safety. The recent position statement by AACE emphasizes that safety and efficacy should be given the highest importance rather than the cost of the treatment.[2] Availability of a food-derived formulation that could safely and effectively

lower HbA1c levels could be an attractive solution for patients with newly diagnosed hyperglycemia. Better acceptability of such an option may also increase adherence, leading to substantial public health gains if these reductions could be sustained in the long term. As part of ESSENS, large-scale, long-term observational studies are already being conceptualized to evaluate the impact of PreCrea® on clinical outcomes.

Limitations

The main limitations of the present study were its relatively small sample size and shorter duration. As a result, it was not possible to determine the long-term clinical outcomes and safety of PreCrea®. Only treatment-naïve patients were included in this study. As a result, the effect of PreCrea®, if any, on the incremental reduction in HbA1c levels in patients already on metformin therapy could not be assessed. Further studies are required to address these limitations.

Conclusion

In conclusion, this study demonstrates the efficacy and safety of PreCrea® in lowering HbA1c, FPG, and TG levels after 12 weeks of treatment in Indian subjects with newly diagnosed hyperglycemia. A nearly 1% point reduction in HbA1c levels observed at week 12 with PreCrea® administration is comparable to the reductions noticed with most oral antidiabetic therapies.[5] There was no safety/tolerability issue observed with PreCrea®. Further large-scale, long-term studies are being conceptualized to determine the impact of PreCrea® on treatment adherence, and finally clinical outcome.

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Conflicts of interest

There are no conflicts of interest.

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