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Double Blind, Randomized Clinical Study to Evaluate Efficacy of Collagen Peptide as Add on Nutritional Supplement in Type 2 Diabetes

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ABSTRACT

Dipeptidyl peptidase IV (DPP IV) inhibitors are currently used to manage Type 2 diabetes mellitus. Peptides derived from collagen has been stated to have DPP IV inhibitory properties. A double blind randomized trial has been conducted to evaluate the effectiveness of collagen peptides (CPT) as nutritional supplement in subjects with type 2 diabetes. Resistant dextrin, a non-digestible dietary polymer, has been used as active comparator in this study. The subjects have been advised to consume 10g per day either CPT or resistant dextrin for 90 days. There is significant reduction in fasting blood glucose (FBG) and HbA1C in three months study period in subjects who have taken oral ingestion of CPT. Insulin sensitivity measured in as HOMA IR has been improved significantly in CPT group. Study demonstrates the potential role of CPT as add on nutritional supplement for the management of type 2 diabetes.

Keywords: Collagen peptide; DPP IV inhibition; Type 2 diabetes; Nutritional supplement

Introduction

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are Incretin hormones responsible for modulating insulin synthesis and secretion and for maintaining the blood glucose at normal levels [1]. Incretin effect refers to the amplification of glucose stimulated insulin secretion elicited by hormones secreted from the gastrointestinal tract. The two Incretin hormones have short half-lives of only 1-2 minutes following their secretion in response to the ingestion of nutrients because of the degradation by the action of Dipeptidyl peptidase (DPP IV). Dipeptidyl peptidase is a serine protease enzyme that specifically acts on Proline or alanine in the second position of the N-terminus polypeptides. DPP IV enzyme can specifically cleave X-Proline or X-alanine from the N terminus of peptides [2,3]. DPP-IV displays a preference for substrates having Proline, Alanine, Serine and Hydroxyproline in sequence as the second N-terminal residue [4,5]. GLP-1 exerts several metabolic effects that regulates glucose homeostasis, including suppression of glucagon secretion, enhancement of glucose disposal, and slowing of gastric emptying. Both GLP-1 and GIP have been shown to increase β-cell mass in animal studies, through the promotion of islet cell growth and inhibition of apoptosis. Several clinical studies have confirmed that concentration of active GIP and GLP-1 are increased by DPP IV inhibitors. GLP-1 amide infusion into human subjects has been shown to stimulate insulin secretion, reduced glucagon secretion and significantly reduced the fasting blood glucose level after meal ingestion. The importance of Incretin effect for the maintenance of glucose homeostasis is clearly established and Incretin based therapies are among the most promising new therapies for type 2 diabetes. In view of this, DPP-IV inhibitors have been demonstrated to be an

effective treatment option for type-2 diabetes [1,6]. DPP IV is present in variety of tissues, particularly epithelial tissues of liver, kidney and small intestines and exists in soluble circulating form.

The bioactive peptides originates from dietary proteins have been recognized to improve various aspects of human health. A wide range of short chain peptides derived from milk, wheat, soybean etc. have been shown to possess DPP IV inhibitory activity [7,8]. Collagen peptides are derived from enzymatic hydrolysis of collagen, a fibrous protein which forms the major part of connective tissue. The amino acid composition of collagen is characterized by repeating sequences Gly-X-Y, where X is mostly proline and Y is mostly hydroxy proline. Collagen peptides represent bioactive peptides that exhibit various physiological activities. Several studies have reported the positive role of collagen peptides in joint health, bone health, skin health etc [9-11].

Collagen hydrolysate has been reported to be the rich sources of DPP-IV inhibitory peptides [7]. Peptides derived from Atlantic Salmon skin Gelatin have been reported to be a beneficial ingredient for functional food against Type 2 diabetes [12]. The peptide sequences Gly-Pro-Ala-Glu and Gly-Pro-Gly-Ala purified from Atlantic Salmon skin Gelatin have been shown to possess DPP IV inhibitory property. A recent study by Jin et al. [13] identified DPP IV inhibitory peptides from deer skin hydrolysate by LC-MS/MS.

Ingestion of Tilapia skin collagen peptides have shown glucose lowering effects in alloxan induced diabetic mice [14]. The study has shown 31.8% reduction of blood glucose in 25 days of experimental period.

Collagen derived peptides have been demonstrated to be source of bioactive peptide with many health benefit. Various studies *in vitro* and *in vivo* have clearly established the potential role of collagen derived peptides in DPP IV inhibitory properties and the prospective effect of collagen peptides in treatment of Type 2 diabetes [15,16]. In view of this, the present study is aimed at a clinical evaluation of collagen derived peptides as add on supplement in management of Type 2 diabetes mellitus.

Resistant Dextrin, a digestion resistant glucose polymer, is used as the comparator in this study as it tends to act as an efficient control on assessing the outcome measures of the clinical study. The double blind study is unbiased and enabling efficient capturing of effectiveness of collagen peptides over the active comparator in reduction of blood glucose levels and overall improvement in quality of life.

Materials and Methods

Investigational Products

Fish collagen peptide (FCP) was supplied by Nitta Gelatin India Limited while the comparator resistant dextrin (Fibersol®, the digestion resistant maltodextrin) supplied by M/s. Brentag Ingredients.

Study design

The study was designed as a double blind, prospective, comparative, randomized, active controlled, two arm clinical study. The investigational products Collagen Peptide were evaluated against an Active control Resistant Dextrin, in a double blinded fashion. The Investigational Product (Collagen Peptide) and Active Control (Resistant dextrin) had been administered orally once a day by dissolving 10g product in 200mL Luke warm water or milk. The subjects were permitted to oral hypoglycemic agents that the subject has been regularly consuming. Thus ethically the subjects were not deprived of a hypoglycemic agent.

Since the Active control is therapeutically effective it will justify all subjects participate in the trial as a nutritional supplement instead of using a placebo with no effect.

A sample size of 60 subjects of male and female who met the study criteria and between the age of 21 to 50 years with known history of diagnosis of Type 2 diabetes were screened and enrolled in the study. As the nature and scale of measurement in this study were more of ordinal in nature, the sample size was governed by the laboratory parameters and the scores of the questionnaire and the Type I (5%) and Type II errors (10%). The numbers of measures, the comparable objectives and the effect size are taken into account in deciding the sample size. In order to accommodate non sampling errors such as nonresponsive or drop outs, an additional 10% of subjects were considered in the study. The enrolled subjects were randomized in a 2:1 ratio as illustrated in Figure 1. The 40 subjects on Collagen Peptide arm and 20 subjects on Resistant Dextrin arm. The randomization schedule was based on SAS generated randomization schedule. All subjects were enrolled either of the treatment arms using double blind code. The study was conducted over a period of 12 weeks with 5 days of run-in period between screening and enrollment with a window period of ±2 days. The run-in period avoids any evaluation interference from any other nutritional supplements that the subjects might be on.

The response to treatment was evaluated by improvements in clinical, laboratory and subjective assessments. Quality of life questionnaire was administered as a baseline evaluation. The subjects were under primary therapy with oral hypoglycemic agents as detailed in Table 1 during the course of study.

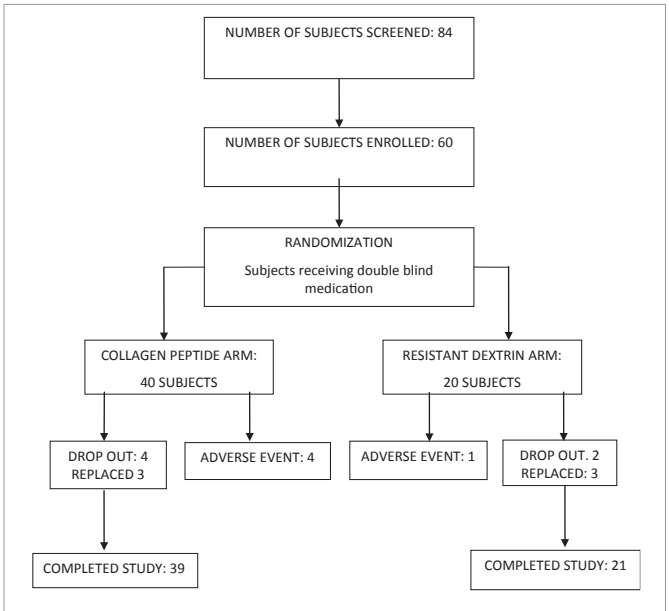

Figure 1: Illustration of selection method of subjects for clinical study and study design. The subjects were randomized after run in period with primary therapy into two arms of Collagen peptide and resistant dextrin in 2:1 ratio.

Table 1: Primary Oral Hypoglycemic agents.

Primary oral hypoglycemic agents
Metformin Hydrochloride 500 mg
Pioglitazone 2 mg Glimepiride 15 mg Metformin 500 mg
Voglibose 0.3 mg
Triglynase Pioglitazone 7.5 mg
Gliclazide 80 mg

Improvement metrics were assessed every 3 weeks. For improvement metrics, Fasting Blood glucose, HbA1C (every 6 weeks) and Quality of life questionnaire were assessed periodically. The study treatment was completed after treatment duration of 12 weeks for each enrolled subject. During the end of the study visit, Fasting Blood Glucose, Glycosylated Hemoglobin (HbA1c), Insulin Sensitivity, Complete Blood Count and Serum Biochemistry were assessed, along with Quality of life questionnaire

The clinical study protocol was planned and developed as per the criteria defined in Section 6 of ICH Harmonized Tripartite Guideline – Guideline for Good Clinical Practice E6 (R1) and Appendix X of Schedule Y of Drugs and Cosmetics Rules 1945, Government of India. Study was conducted after approval from Universal Ethical committee an independent ethical committee located at Chennai, India where the study has been conducted after getting written informed consent from all subjects. The trial was registered with Clinical Trial Registry India with registration No. CTRI/2015/02/005518; date: February 10, 2015, National Institute of Medical Statistics, Indian Council of Medical Research, Government of India.

There was no change in the study procedures or conducting after commencement of the study and hence no analysis has been planned or conducted.

Statistical analysis

All statistical testing was performed at the p=0.05 level of significance (two sided). This was a confirmatory study and therefore no adjustments were made for multiple comparisons. All the data was summarized by treatment groups, after un-blinding following completion of the entire study (treatment duration) for all the enrolled subjects.

Change from baseline in study specific parameters was analyzed using an Analysis of Variance (ANOVA) method with treatment group as fixed factors. McNemar's test was used to compare between baseline and end of the treatment weeks. Detailed listings were produced for all study data. All analysis was performed using SAS V 9.1.3. The 95% of confidence interval around the percentage mean change from baseline to end of treatment period was constructed.

Results

Total 39 subjects in CPT group and 21 subjects in Resistant dextrin group completed the study (Figure1). The demographic characteristics are recorded in Table 2. All the patients were advised to follow the routine diet whatever they practiced at the time of inclusion into the clinical study.

The Fasting Blood Glucose (FBG) and Glycosylated Hemoglobin (HbA1c) levels are shown in Figure 2. There is significant reduction in FBG in subjects orally ingested with Collagen Peptide (CPT). It is also observed that their FBG levels are reaching normal levels.

While in case of subjects under Resistant Dextrin (RD) group, although there is reduction in FBG level, the rate of reduction in FBG level is lower compared to that of CPT group.

The levels of HbA1c significantly reduced during the three month treatment period both in CPT and RD groups. The significantly reduced levels of FBG and HbA1c indicate that the glucose metabolism

Table 2: Demographic characteristics.

Variable	Demographic Data	Baseline Data
Male	25	
Female	35	
Height, Unit: cm		**FBG, Unit: mg/dL**
Average	156.8	160.5
Standard deviation	9.8	45.3
Maximum	176	441
Minimum	138	131
Weight, Unit: Kg		**HbA1c, Unit: %**
Average	67.4	7.8
Standard deviation	10.3	1.3
Maximum	95	15.9
Minimum	44	6.5
BMI, Unit: Kg/m		**HOMA-IR, Units**
Average	27.4	6.9
Standard deviation	3.8	0.8
Maximum	32.0	10.2
Minimum	18.7	6.0

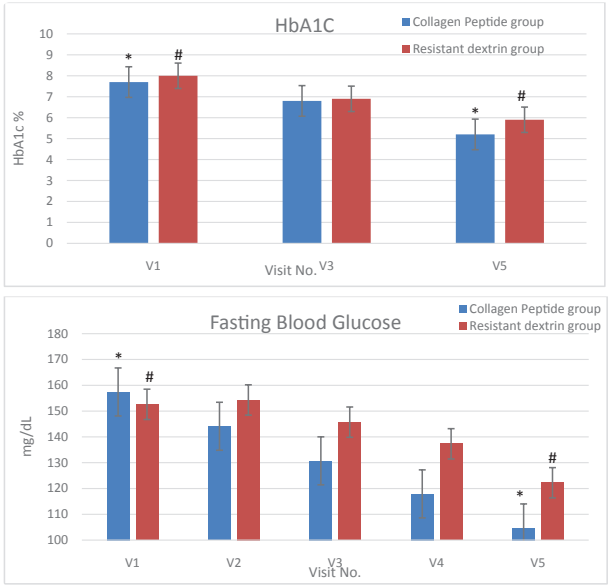

Figure 2: The data are average value with standard deviation; there is significant improvement in FBG and HbA1C from Visit 1(V1) to Visit 5 (V5), p< 0.05 in both Collagen peptide group* and in Resistant dextrin group#.

is improved in CPT treated subjects. A significant reduction in insulin resistance in terms of HOMA-IR measurement has been observed in both the study groups (Figure 3).

In intergroup comparison, the results show that percentage of improvements is significantly higher in CPT group compared to RD groups as per the data in the Figure 4. This difference in efficacy levels indicates the difference in mechanism of action of between CPT and RD. CPT has been found to be more effective in management of glucose metabolism in Type 2 diabetes.

Biochemical evaluations

As part of safety assessment, laboratory analysis was performed for the various biochemical parameters in serum and urine. The results of the Visit 1 and Visit 5 are shown in Table 3. Other than some minor changes none of the biochemical parameters showed significant variation in the results during the study period. The minor changes observed were not clinically significant. All the data were statistically analyzed and found no significant differences from the normal range both the study groups. These findings have demonstrated the safety of CPT in humans. Moreover the US Food and Drug Administration (US FDA) has classified gelatin and collagen peptide as a Generally Recognized as Safe (GRAS) product.

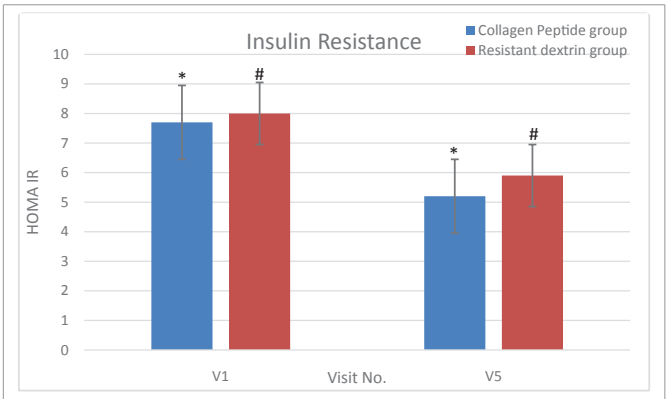

Figure 3: The data are average value with standard deviation; there is significant reduction in Insulin resistance measured as HOMA IR from Visit 1 (V1) to Visit 5 (V5), p< 0.05 in both Collagen peptide group* and in Resistant dextrin group#.

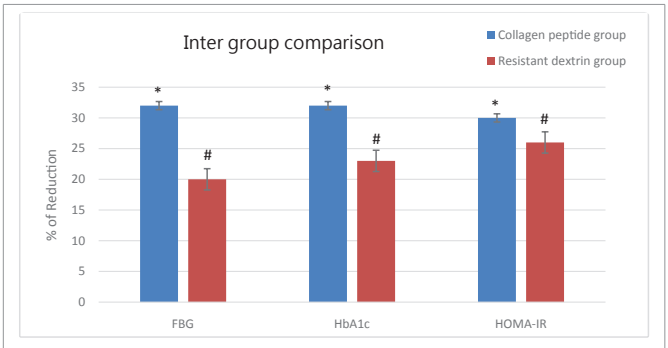

Figure 4: The data are average value with standard deviation for FBG, HbA1c and HOMA-IR; Percentage of reduction is high in CPT* group compared to RD# group: p< 0.05.

Table 3: Serum Biochemistry test results.

Parameters	Unit	Collagen Peptide		Resistant Dextrin	
		Visit 1	Visit 5	Visit 1	Visit 5
Urea	mg/dL	23.6 ± 9.5	31.1 ± 5.7	16.4 ± 7.7	24.0 ± 8.7
Serum creatinine	mg/dL	0.7 ± 0.3	0.9 ± 0.2	0.6 ± 0.4	1.0 ± 0.2
Serum Uric acid	mg/dL	3.0 ± 1.5	3.5 ± 0.9	2.4 ± 1.7	4.2 ± 0.7
SGOT	IU/mL	24.7 ± 11.9	27.1 ± 6.6	16.5 ± 9.0	25.5 ± 7.6
SGPT	IU/mL	20.5 ± 8.9	25.0 ± 5.0	16.8 ± 9.9	26.8 ± 6.9
Alkaline Phosphatase	IU/mL	120.2 ± 40.2	160.4 ± 41.3	112.8 ± 31.9	107.5 ± 16.0
Albumins	g/dL	3.3 ± 1.6	4.3 ± 0.3	4.1 ± 0.2	4.1 ± 0.6
Globulins	g/dL	2.7 ± 1.2	3.5 ± 0.5	3.2 ± 0.4	3.4 ± 0.3
A/G Ratio	-----	1.2 ± 0.3	1.0 ± 0.5	1.3 ± 0.2	1.2 ± 0.2
GGTP	IU/mL	23.9 ± 7.4	33.8 ± 12.8	22.3 ± 9.8	30.5 ± 8.5
Total Serum bilirubin	mg/dL	0.5 ± 0.2	0.7 ± 0.2	0.5 ± 0.3	0.7 ± 0.2
Serum bilirubin (direct)	mg/dL	0.1 ± 0.03	0.1 ± 0.07	0.1 ± 0.05	0.1 ± 0.0
Serum bilirubin (indirect)	mg/dL	0.3 ± 0.1	0.5 ± 0.1	0.3 ± 0.2	0.5 ± 0.1

*The data are mean ± standard deviation.

Adverse events

Out of 66 subjects, 6 subjects were dropped out from the study due to loss follow up. Five subjects, four subjects in CPT group and one subject in comparator group, displayed minor adverse events namely vomiting, cough, dizziness and stomach upset (Figure 1). The incidents were ruled to have a possible causal relationship with the investigational product/comparator. However, there was no change in the dose of the investigational product and subject was not withdrawn from the study. Upon re-challenging the events did not reappear. All events were resolved without sequel. Overall, Collagen Peptide was found to be clinically safe for consumption as add on therapy for the management of diabetes mellitus type 2.

Discussion

Proteins are well known precursors of bioactive peptides showing physiological effects in the body in addition to the nutritional value. Therefore, food derived proteins can be used as potent and safe therapeutic agent in management of several form of diseases. Peptides derived from collagen have been shown to possess DPP IV inhibitory property, which is an important mechanism in the treatment of Type 2 diabetes. The inhibition of DPP-IV is a treatment pathway [17] to increase the level of Incretin hormones and subsequent insulin sensitization to control the blood glucose level. The present study has been carried out to establish the effect of collagen peptides as add on food supplement in management of Type 2 Diabetes. The results of the study have demonstrated that oral ingestion of collagen peptide is effective in controlling the diagnostic parameters of Type 2 Diabetes. There is significant improvements in the FBG levels, HbA1c and insulin sensitivity compared to subjects ingested with resistant dextrin. All the subjects have been in primary therapy during the period of clinical study. The present study is the first of its kind to compare with an active comparator resistant dextrin. The reduced levels of FBG and HbA1c coupled with increase in insulin sensitivity in subjects orally

ingested with collagen peptides demonstrates anti-diabetic properties of collagen peptide by increasing the active GLP-1 level, possibly by inactivation of DPP-IV. DPP-IV specifically acts on a proline (Pro) or alanine in the second position of the N terminus of polypeptides. The presence of a Pro residue in a given peptide is a good indicator of its DPP-IV inhibitory properties [18] of peptides derived from Collagen.

Dominant sequence of collagen is a continuous repeating sequence of Gly-X-Y triplets, where X is mostly proline and Y is mostly hydroxyproline. Peptides with proline as the penultimate N-terminal residue have shown to possess DPP IV inhibitory activity in Streptozotocin induced diabetic rats [19]. Recent study by Iba et al. [20] showed that collagen peptides similar to those used in this study have DPP IV inhibitory activity and the stimulation of GLP-1 secretion *in vitro,* and evaluated the anti-diabetic properties of collagen peptides in animal models. The authors observed that co-administration of collagen peptides (3g/Kg) with glucose (4g/Kg) significantly increased active GLP-1 levels in the plasma after 15 min while the administration of collagen peptides 45 minutes before glucose, potentiated the glucose stimulated secretion of insulin.

A study in Chinese subjects with Type 2 Diabetes, treatment with marine collagen peptide, a significant reduction in levels of fasting blood glucose, glycosylated hemoglobin and increased level of insulin sensitivity were observed [21]. While the study further confirms the evidence of anti-diabetic role of peptides derived from collagen, the outcome of measurements has not reached to the level compared to the observations in the present study. The reason could be attributed to the differences in active peptide characteristics in the collagen derived peptides. The significant reduced level of HbA1c and increase in level of insulin sensitivity observed in subjects ingested with collagen peptide in the present study suggests that oral ingestion of collagen peptide has resulted in improved glucose metabolism in diabetic subjects.

There is significant outcome in subjects orally ingested with resistant dextrin in three months study period. Soluble fiber, such as Resistant dextrin by prolonging the transit time through the gastrointestinal tract and reducing the rate at which nutrients are digested and absorbed from the small intestine, viscous fibers are able to increase satiety and attenuate postprandial glucose response. The positive effect of reducing the postprandial glycaemia by viscous fibers may have role in managing the Type 2 diabetes [22]. The beneficial role of resistant dextrin is the delayed rate at which the glucose is absorbed from the small intestine. In this study, the improvement in subjects ingested with collagen peptide is significantly better compared to subjects who took oral consumption of resistant dextrin.

The study further demonstrates efficacy of collagen peptide over resistant dextrin. Possibly the difference in efficacy level is associated with the differences in mechanism of action. Both resistant dextrin and collagen peptide are categorized as food supplements with functional properties. The role of resistant dextrin is to delay the rate of glucose absorption while that of collagen peptide is improving insulin sensitivity, may be by promoting the activation of Incretin hormones through DPP IV inhibition pathway, the strategic treatment method in the management of Type 2 diabetes. Being the bioactive peptide derived from protein, collagen peptide as food supplement has significant importance in the treatment of type 2 diabetes in view of some negative impacts of daily consumption of functional fibers which may lead to reduction in drive for food and subsequent weight loss.

Conclusion

To summarize, the present study clearly established the efficacy of collagen derived peptides as add on supplement in the management of Type 2 diabetes mellitus. The reduction of FBG and HbA1c to the normal levels during the end of study period in the study subjects who were given oral supplementation of collagen derived peptides demonstrate that collagen peptide as one of the emerging treatment option to reduce the dosage of various types of drugs in treatment of Type 2 diabetes and thereby minimizing the deleterious effects of such drugs.

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