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Evaluating Role of Cholagogue and Choleretic Drugs in the Management of NIDDM Related to Post Cholecystectomy - A Pilot Clinical Trial

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Abstract

Diabetes becomes a global health burden, affecting almost one third of world population. This figure is self explanatory for its alarming growth and concern to be given for its prevention and management. It is erroneous to treat it as a disease rather it should be treated as a syndrome, because rarely it is presented in its discrete form i.e. only hyperglycemia as a clinical feature. Being a metabolic disease it is almost always accompanied with many other diseases like hypothyroidism, hypertension, fatty liver disease, obesity, dyslipidemia, etc. According to the known pathophysiology of diabetes, hyperglycemia is said to be responsible for dyslipidemia, constant high sugar level in blood produces dreaded effect at micro as well as macro- vascular level. This established pathology of the disease revolves around high glucose level in blood and make it the diagnostic parameter for diabetes. Although the cause of hyperglycemia are also well defined but there is one missing link which is totally neglected by the modern science i.e., role of liver in the pathogenesis of diabetes. Do any way hampered liver functions affect insulin production or its utilization by the cell- the question that required answer. This clinical trial is based on materializing the concept that effective bile secretion improves insulin activity. This is a pilot study carried out on 15 known patient of non insulin dependent diabetes. The study showed that 66.6% patient has diabetes associated with hypothyroidism followed by dyslipidemia (60%). The study drug shows significant ($p < 0.001$) reduction in both FBS and PPBS and improve the presenting symptoms effectively.

Keywords: Bile, Dyslipidemia, Hyperglycemia, Insulin

1. Introduction

Undoubtedly diabetes is related to hyperglycemia but diabetic patients may also suffer severe complications due to disturbed physiological and biochemical processes associated with the disturbed bile acids production and microfloral composition[1–6]. Use of bile acids in diabetes treatment is now a day encouraging because it is found to improve glycemia as well the ameliorate complications. A long waited major improvement would be the discovery of treatments for diabetes that avoid and even replace the absolute requirement for injected insulin. Recent studies in a rat model of Type 1 diabetes show that a multi-therapeutic approach incorporating bile acids and probiotics, as adjunct therapy, exerted better control over glycemia and resulted in ameliorating complications, than when each treatment was administered alone[7,8]. Accordingly, improving diabetes complications, reducing prevalence and restoring normal physiological patterns

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should significantly optimise diabetes treatment and the quality of life of diabetic patients.

In the past, bile acids were considered to have three basic physiological functions[9,10]:

- Elimination of excess cholesterol.
- Facilitation of the digestion of dietary fats (emulsifying agents).
- Facilitation of the absorption of fat soluble vitamins such as A, D and K.

However, recent studies have expanded the role of bile acids to include endocrine signaling to regulate glucose, lipid and their own homeostasis and influence energy expenditure and gut microfloral composition.

Hepatic fat accumulation is a well-recognized complication of diabetes with a reported frequency of 40–70 %. Impaired gall bladder contraction was found amongst patients of diabetes mellitus with autonomic neuropathy. The mechanism responsible for cholecystoparesis is attributed to vagal neuropathy. Incomplete gall bladder emptying leads to sequestration of cholesterol and nidus formation. Patients of diabetes mellitus had statistically significant larger fasting gall bladder volumes and these values were highly significant amongst patients with autonomic neuropathy. 2. Patients of diabetes mellitus and statistically significant larger post fatty meal gall bladder volume and these values were highly significant in patients with autonomic neuropathy[11].

2. Relation between Disturbed Bile Salt Concentration and Diabetes

The amino acid taurine, which is used by hepatocytes in bile acid conjugation and bile salts formation, has many other physiological functions including the regulation of intracellular osmolarity, cardiomyocytes functions, and as an antioxidant. A hypoglycemic effect of taurine, directly or through synergizing the effect of insulin, has also been reported[12]. Conjugated bile acids include glycine and taurine conjugates, both existing in constant ratio. Glycine conjugated bile acids are less soluble and are harder to excrete compared with taurine conjugated bile acids. This result in bile accumulation noticed in diabetic subjects[13]. In diabetic patients, who have increased lipid metabolism, the percentage of taurocholic acid in bile is decreased indicating an altered biosynthesis of taurine[14].

Conjugated bile acids (bile salts) can form micelles that solubilise and transport lipids across biological membranes. Bile acids as absorption promoters have the potential to aid intestinal, ocular, nasal, pulmonary and rectal absorption of insulin. Bile acids are hypoglycemic agents on their own and thus can be used as adjunct therapy in treating Diabetes.

Therefore it is clear that disturbed composition as well as secretion of bile causes improper absorption of insulin and impaired elimination of cholesterol and digestion of dietary protein. This leads to Steatohepatitis and secondary Insulin resistance. Thus impaired bile secretion with improper composition causes fatty liver, dyslipidemia and hyperglycemia.

According to Ayurveda the pathogenesis of *Prameha* starts with the vitiation of *Meda* by *Kapha* followed by *Mamsa* and other *dushya* and then only vitiation of *Mutra* to manifest as *Prameha*. This signifies that according to Ayurveda Hyperglycemia preceded by Dyslipidiemias. The role of *Meda* (fat/adipose tissues) is of great importance in the pathogenesis of *Prameha*. Its role is not as *Dushya* (disturbed functioning of the dhatus), but something more than that. According to Charaka Samhita, *Vapavahana* and *Vrikka* are the *Srotomula* of *Meda dhatu*. It is important to elaborate the term *Vapavahana* in the context of *Prameha* as the vitiated *dhatu* causes vitiation of *Srotas* and vice-versa. Vapavahan signifies an organ responsible for circulation/storage of Vasa/ Meda. It can be correlated with Gall Bladder. The next important pathological hallmark in the pathogenesis of *Prameha* is *Bahudrava Shleshma* (*Kapha* that contains too much liquid) that joins and affects *Meda*, causing it to become *Abaddha* (unobstructed or fluid). *Bahudrava* means that *Kapha* loses its natural properties and get vitiated; it is worth full to mention here that this derangement may be acquired (due to faulty dietary habits and life style) or congenital, whatever may be the cause this vitiated *Kapha* is unable to perform its normal functions. Describing the physical properties of *Kapha* it is mentioned that it is unctuous in touch and look like *ghrta* (oil). Thus it can be said that *Kapha* in body represents lipid components of the body and vitiated *Kapha* can be correlated with dyslipidemia.

Role of dyslipidemia and metabolic abnormalities in the pathogenesis of diabetes is very obvious and well elaborated in modern medicine. Among the metabolic abnormalities that commonly accompany diabetes are disturbances in the production and clearance of plasma lipoproteins. Moreover, development of dyslipidemia may be a harbinger of future diabetes. A characteristic pattern, termed diabetic dyslipidemia, consists of low High Density Lipoprotein (HDL), increased triglycerides, and postprandial lipemia. This pattern is most frequently seen in type 2 diabetes and may be a treatable risk factor for subsequent cardiovascular disease[15–17]. Thus Ayurveda says that disturbed secretion of bile by Gall Bladder causes improper lipid metabolism that secondarily leads to Diabetes.

The contemporary hypoglycemic drugs gives good glycemic control in newly diagnosed cases but in chronic cases there is no alternative than using Insulin due to which the term NIIDM is not use these days. Increasing the dose or synergistically administration of one or more neither hypoglycemic drugs nor control the glucose level neither prevents complications. A patient of Diabetes with fatty liver, Dyslipidemia and autonomic neuropathy can't be only manage by hypoglycemic drugs only and therefore with the progression of disease and manifestation of complications its management become more and more difficult. The established Ayurvedic anti-diabetic drugs like Vijaysara (ICMR study) showed that it has no effect on Cholesterol, LDL, VLDL and ALT, AST.

Therefore we plan to carry out a clinical trial to evaluate the effect of Cholagogue and Choleretic drugs in the management of type-2 Diabetes and simultaneous assess its effect on liver function and lipid profile. This clinical study will helpful in establishing a safe, cost effective, well tolerated and multitargeted drug which is effective to manage hyperglycemia, fatty liver and dyslipidemia concurrently with evidences.

In the present study we have chosen four drugs which are found to have Cholagogue and Choleretic effect in experimental studies. These drugs are – *Kutaki, Bhringaraj, Bhumanlaki* and *Kalmegha.*

Research studies have shown that Picrorhiza kurroa has a dose-dependent (1.5-12 mg/kg x 7) choleretic effect; it also possessed a marked anticholestatic effect against paracetamol- and ethynylestradiol-induced cholestasis[18]. It antagonized the changes in bile volume as well as the contents (bile salts and bile acids). It has also reported to have hypoglycemic activity[19]. *Bhumyamalki* is reported for having potent hepatoprotective, immunostimulating, antiinflammatory, antiviral, antioxidant, cholagogue, adaptogenic and membrane stabilizing properties, which are constitutive qualities for any hepatoprotective drugs to act against viral hepatitis[20,21]. These activities have been attributed to its anticholestatic action, reduction in free radicals and reduction in cell protein necrosis as well as immune suppression and glutathione depletion reduction potential. Phyllanthus niruri is also claimed to have anti-diabetic effect[22]. Previous research studies showed that Eclipta alba has significant Cholagogue hepatoprotective activity against paracetmol induced rat. The antiheptotoxic activity of the leaf extract of Eclipta alba were compared with the standard hepatoprotective agent silymarin[23]. Eclipta alba is also reported to have hypoglycemic activity[24]. *Kalmegha* is known as King of Bitter and is reported to have a wide range of medicinal and pharmacological actions. Previous studies showed the Choleretic effect of Andrographolide obtained from Andrographic panniculata in rats[25]. It also has antioxidant and hepatoprotective effect[26].

3. Aim and Objective

- To assess the effect of PEPA compound in the management of Type-2 Diabetes Mellitus.

3.1 Inclusion Criteria

- Patients of either sex aged between 30 to 65 years
- Treatment naive patients or diagnosed patients of Type II Diabetes Mellitus taking oral hypoglycemic drugs for ≤ 6 weeks
- Patients having Glycosylated haemoglobin (HbA1c) ≥ 6.5% - 8%.
- Willing and able to participate for 16 weeks

3.2 Exclusion Criteria

- Patients already diagnosed to be suffering from the severe complications of Diabetes Mellitus viz.,

diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, etc.

- Patients suffering from brittle diabetes mellitus.
- Patients who have a past history of Atrial Fibrillation, Acute Coronary Syndrome, Myocardial Infarction, Stroke or Severe Arrhythmia.
- Patient with poorly controlled Hypertension ($\geq$ 160 / 100 mm Hg)
- Symptomatic patient with clinical evidence of Heart failure.
- Patients with concurrent serious Hepatic Dysfunction (defined as AST and/or ALT > 4 times of the upper normal limit) or Renal Dysfunction (defined as S. creatinine > 1.2 mg/dl), uncontrolled Pulmonary Dysfunction (asthmatic and COPD patients) or other concurrent severe disease.
- Pregnant/Lactating women.
- Patient on steroids, oral contraceptive pills or estrogen replacement therapy.
- Alcoholics and/or drug abusers.
- Patients with evidence of malignancy
- Patients suffering from major systemic illness necessitating long term drug treatment (Rheumatoid arthritis, Psycho-Neuro-Endocrinal disorders, etc.)
- H/o hypersensitivity to any of the trial drugs or their ingredients.

Table 1: Content of PEPA compound

Name of the Drug	Botonical name	Part Uesd	Approx. quantity in 500mg of Capsule
Kutaki	Picrorhiza kurroa	*Moola* (Root)	250mg
Bhringraj	Eclipta alba	*Panchanga* (whole plant)	250mg
Bhumiamalaki	Phyllanthus niruri	Whole plant	250mg
Kalmegha	Andrographis paniculata	Whole plant	250mg

3.3 Study Groups

This was a pilot study to evaluate the efficacy of polyherbal compound in management of T2 Diabetes mellitus and therefore only 15 patients were enrolled in the study and allocated in a single group.

3.4 Study Duration

The study was conducted at the O.P.D and I.P.D. wing of Chaudhary Brahm Prakash Ayurveda Charak Sansathan, Khera Dabur, New Delhi between March 2015 to September 2015.

4. Assessment Parameters

4.1 Subjective Parameters

- Bahumutrata (polyuria).
- Aavilamutrata (discoloration of urine/ change in consistency of urine)
- Kara-pada Daha (burning sensation in palm & sole)
- Kara-pada Suptata (numbness in hands & feet)
- Pipasa (polydipsia)
- Mukhatalu-kantha sosha (dryness of mouth & throat)
- Kshudha Adhikya (polyphagia)
- Aalasya (fatigue)
- Dhatukshaya (unexplained weight loss)
- Kayachidreshupdeha (blurred vision)

4.2 Objective Parameters

- Fasting blood sugar
- Postprandial blood sugar

5. Observation and Result

The table 2 reveals that *Bahumutrata* was found in 86.6% patients, *Pipasa, Mukhatalu-kantha sosha, Aalasya* and *Kayacchidreshupdeha* in 80% patients, *Dhatukshaya* in 73.3%,

Karapadadaha in 60% patients, *Kara-pada Suptata* in 46.6% patients, *Aavilamutrata* and *Kshudha Adhikya* in 40.0% patients.

Table 2: Clinical sign and symptoms observed in patients

S.No.	Signs & Symptoms	Number of patients	Percentage
1.	*Bahumutrata* (polyuria)	13	86.6
2.	*Aavilamutrata* (discoloration of urine/ change in consistency of urine)	6	40.0
3.	*Kara-pada Daha* (burning sensation in palm & sole)	9	60.0
4.	*Kara-pada Suptata* (numbness in hands & feet)	7	46.6
5.	*Pipasa* (polydipsia)	12	80.0
6.	*Mukhatalu-kantha sosha* (dryness of mouth & throat)	12	80.0
7.	*Kshudha Adhikya* (polyphagia)	6	40.0
8.	*Aalasya* (fatigue)	12	80.0
9.	*Dhatukshaya* (unexplained weight loss)	11	73.3
10.	*Kayacchidreshupdeha* (blurred vision)	12	80.0

Table 3: Associated Diseases observed in 15 diagnosed Patients of *Prameha*

S. No.	Associated Diseases	Number of Patients	Percentage
1.	Cholelithiasis/ Cholecystectomy	6	40.0
2.	Obesity	7	46.6
3.	Dyslipidemia	9	60.0
4.	Hypothyroidism	10	66.6
5.	Hypertension	8	53.3
6.	Fatty Liver Syndrome	8	53.3

Oral medicine group provided highly significant ($p<0.001$) reduction in blood sugar level fasting and post prandial. While provided significant result in fasting sugar while highly significant reduction in postprandial level.

The Table 5, shows that highly significant (<0.001) improvement were found in *Bahumutrata, Kara-pada Daha, Mukhatalu-kantha sosha, Aalasya and Dhatukshaya* whereas significant improvement were noted in *Aavilamutrata, Kara-pada Suptata, Pipasa and Kshudha Adhikya.*

6. Discussion

According to the concept of Ayurveda there are two types of *Prameha* (diabetes) *Avarana janya madhumeha* and *dhatu kshya janya madhumeha*, it supports the receptor theory of modern medicine. Addition of Ayurvedic medicaments as supportive therapy to the NIDDM patients decrease the requirement of exogenous insulin thus ultimately helping in reducing adverse effects

Table 4: Clinical efficacy of PEPA compound on blood sugar level of 15 Patients

S. No.	Blood Sugar Level mg/dl	Mean Score		S.D.	S.E.	't'	P
		BT	AT				
1.	Fasting Blood Sugar	226	158.8	47.51	33.6	3.66	<0.001
2.	Post Prandial Blood Sugar	334.8	235.7	70.07	49.55	3.12	<0.001

Table 5: Clinical efficacy of PEPA compound on subjective parameters

S. No.	Signs & Symptoms	Mean Score		(%)	S.D. (+)	S.E. (+)	't'	P	Result
		BT	AT						
1.	*Bahumutrata* (n=13)	2.34	0.50	78.6	0.89	0.21	8.28	<0.001	H.S
2.	*Aavilamutrata* (n=6)	1.90	0.50	71.60	0.95	0.45	2.56	<0.05	S
3.	*Kara-pada Daha* (n=9)	2.12	0.47	76.4	0.92	0.28	8.02	<0.001	H.S
4.	*Kara-pada Suptata* (n=7)	2.18	1.27	41.66	1.04	0.31	2.88	<0.01	S
5.	*Pipasa* (n=12)	2.33	0.53	77.14	1.01	0.26	6.87	<0.001	H.S
6.	*Mukhatalu-kantha sosha* (n=12)	2.36	0.46	77.77	0.65	0.18	8.50	<0.001	H.S
7.	*Kshudha Adhikya* (n=6)	2.18	1.27	41.66	1.04	0.31	2.88	<0.01	S
8.	*Aalasya* (n=12)	2.18	0.56	67.21	0.76	0.16	8.60	<0.001	H.S
9.	*Dhatukshaya* (n= 11)	2.08	0.50	75.33	0.63	0.16	8.95	<0.001	H.S

caused by insulin therapy. Acharya Sushruta described *Apathya nimittaja Prameha* which is nearer to type 2 diabetes. It emphasizes on diabetes- insulin toxicity-hyper insulinemia-obesity. On the other hand Ayurveda also give a due emphasis to *Prameha-sthaulya* (*Sthula Pramehi*)- importance of *Meda* (lipids) among 10 *dushyas* etc. Moreover, Sushruta advocates *Medoroga chikitsa* (obesity) in *Prameha chikitsa* highlighting closeness between *sthaulya* (obesity) and *Prameha*(diabetes). Though Prameha is more than diabetes as it covers obesity-diabetes-metabolic syndrome all together but the concept given by in old Indian Medical treatise for management of Prameha is well applicable for diabetes also. Basically body rely upon its own endogenous synthesis and if anything supplement from outer source it not only reject it but also stops its own production. So it is more useful to potentiate body own production by strengthening its own powerhouse i.e., liver which may be either by burning excessive fat deposited in its cells (through exercise) or by rejuvenating it by using cholagogue and cholerectic drugs.

7. Conclusion

This is a very preliminary type clinical study and thus not able to give any definitive conclusion but then also it proves to be a footstep guiding those who are interested to search new dimension for the management of diabetes.

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