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Original Article

Internal Medicine Section

Comparison of *Nisha-amalaki* and Metformin in Overweight and Obese Patients with Type 2 Diabetes Mellitus (*Madhumeha*): A Randomised Controlled Trial

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is considered a metabolic syndrome marked by an increase in blood sugar level brought on by absolute or relative insulin deficiency, insulin resistance, or both. It was predicted that 171 million individuals would develop type 2 diabetes at the turn of the century; by 2030, this figure is expected to reach 360 million. *Nisha-amalaki* is a commonly used medication for Type 2 Diabetes Mellitus, and its ingredients are also routinely used worldwide. There are numerous studies on *Nisha-amalaki* showing its antidiabetic effect, but it has not been studied in overweight and obese Type 2 diabetic patients; hence, present study is planned.

Aim: To compare the efficacy of *Nisha-amalaki* and Metformin in overweight and obese patients with Type 2 Diabetes Mellitus.

Materials and Methods: The present was a parallel-group, single-blind, randomised, standard controlled trial conducted in the Department of Kayachikitsa, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India. The trial included a 60-day treatment period and a follow-up period every 15 days. The study comprised a total of 60 overweight and obese patients suffering from *Madhumeha*, randomly divided into two equal groups. Group N (experimental group) was treated with 6 gm *Nisha-amalaki Churna* two times a day before meals with lukewarm water, and Group M (control group) was treated with 1 gm Tablet Metformin administered twice a day before meals in equal divided doses for 60 days. Patients were assessed for objective parameters like Fasting Blood Sugar (FBS) level, Post Meal Blood Sugar (PMBS) level, and Body Mass Index (BMI) at the start and end of the study. Statistical analysis was done by assessing through paired and unpaired t-tests and compared with the help of Z-test.

Results: *Madhumeha* is more prevalent in the 51-60 years age group as well as in males compared to females. The mean FBS level before treatment was 151.98 mg/dL and 143.08 mg/dL in Group M and Group N, respectively, which significantly reduced to 138.56 mg/dL and 129.39 mg/dL after treatment. The mean PMBS level before treatment was 232.45 mg/dL and 223.56 mg/dL in Group M and Group N, respectively, which reduced to 230.35 mg/dL and 209.26 mg/dL after treatment. The mean BMI before treatment was 26.49 mg/dL and 26.06 mg/dL in Group M and Group N, respectively, which reduced to 26.23 mg/dL and 25.86 mg/dL after treatment. Both the groups (standard as well as the trial group) are equally effective in reducing FBS level. During the follow-up visits, no adverse effects or side effects were observed in any patient.

Conclusion: Both *Nisha-amalaki Churna* and Tablet Metformin are equally effective in reducing FBS level. *Nisha-amalaki* has a better effect compared to Metformin in reducing PMBS level. Metformin has a better effect compared to *Nisha-amalaki* in reducing BMI. So, it can be concluded that *Nisha-amalaki Churna* is as effective as Tablet Metformin in the management of overweight and obese patients suffering from Type 2 Diabetes Mellitus.

Keywords: Churna, Fasting blood sugar level, Post meal blood sugar level

INTRODUCTION

Type 2 Diabetes Mellitus is considered a metabolic syndrome marked by an increase in blood sugar level brought on by absolute or relative insulin deficiency, insulin resistance, or both [1]. In developing and middle-income nations like India, type 2 diabetes mellitus is a potentially epidemic health problem that is growing rapidly. By 2025, estimates indicate that there will be 69.9 million cases of diabetes in India, the vast majority of which will remain untreated [2]. It was predicted that 171 million individuals would develop type 2 diabetes at the turn of the century; by 2030, this figure is expected to reach 360 million [3].

Metformin has been the drug of choice for disorders related to Type 2 Diabetes Mellitus, overweight, and age-related disorders due to its excellent tolerability, safety profile, and efficacy in decreasing blood sugar levels [4]. In the classical texts of Ayurveda, out of the twenty types of *Prameha*, the clinical features of *Madhumeha* are matchable with Type 2 Diabetes Mellitus. Therefore, *Madhumeha* can be correlated with Type 2 Diabetes Mellitus [5].

Nisha-amalaki is one of the common medicines mentioned in various *Samhitas* for the management of *Madhumeha*, namely *Charak, Vagbhat*, and *Sushrut* [6-8]. It is needed to explore safer medicine. *Nisha-amalaki* is a commonly used medication for Type 2 Diabetes Mellitus, and its ingredients are also in routine use worldwide. There are numerous studies on *Nisha-amalaki* showing its antidiabetic effect, but it has not been studied in overweight and obese Type 2 diabetic patients; hence, present study was planned [9-11]. The research protocol for present study has already been published [12].

The aim of present study was to compare the efficacy of *Nisha-amalaki* and Metformin in overweight and obese patients with Type 2 Diabetes Mellitus.

MATERIALS AND METHODS

A parallel-group, single-blind, randomised standard controlled trial was conducted with patients who visited the Outpatient and Inpatient Departments of the Kayachikitsa Department, Datta Meghe Institute of

Higher Education and Research, Wardha, Maharashtra, India as well as those from specialty camps, registered for the present study over a duration of two years and six months. The study was completed in June 2023. Approval was obtained from the Institutional Ethics Committee (Ref no. MGACHRC/IEC/July- 2021/331). The study was started after registration with CTRI (Reg. no. Clinical Trail Registry (CTRI)/2021/10/037263). Before the commencement of the study, written informed consent was taken from each patient.

Inclusion criteria: Patients aged between 30 to 60 years of either gender, with FBS Level more than 126 mg/dL and/or postprandial blood sugar level more than 200 mg/dL, and BMI between 25-30 kg/m^2 [13].

Exclusion criteria: Patients with FBS level more than 200 mg/dL, postprandial blood sugar level more than 300 mg/dL, pregnant and lactating women, patients with acute complications like cirrhosis of the liver, pancreatitis, and hypoglycaemic shock, and those with chronic complications like nephropathy, retinopathy, and neuropathy were excluded from the study.

Sample size calculation: The sample size was calculated by software and master 2.0. There were two proportions; Hypothesis testing-large population and in equal allocation. Proportion in group M was 0.85, proportion in group M was 0.5483. The risk difference=0.3017, power (%)=80, alpha error (%)=5, side=2 and required sample size for each group was 27.

Dropout–10% thus By considering 10% dropout rate.

Sample size×Dropout factor=Total number of patients to be taken 27×1.11=30 patients.

Each group had 30 patients.

Total sample size was of 60 patients.

Study Procedure

In present trial, a total of 60 patients were chosen for the research, divided into two equal groups of 30 patients each. Participants met the criteria for randomisation and were assigned to the experimental and control groups in a 1:1 ratio. A lottery method of randomisation mechanism provided researchers with access to the treatment allocation for each eligible participant, ensuring that the patients were kept blinded.

Group N was the experimental group, whereas Group M was the standard controlled group. The objective parameters studied in the trial include FBS level, PMBS level, and BMI before starting and at the end of the study.

Primary outcomes with significant improvement was seen in both groups in reducing the objective parameters, including FBS levels, PMBS levels, and BMI in overweight and obese patients suffering from Type 2 Diabetes Mellitus *(Madhumeha)*.

Secondary outcomes with no adverse effects of the trial drug were observed in any patients enrolled in present study.

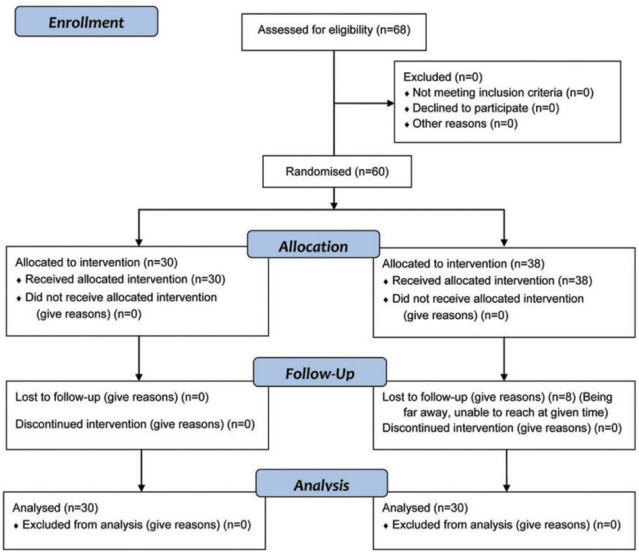
The grouping and posology for *Nisha-amalaki Churna* and Tablet Metformin are mentioned [Table/Fig-1] [14,15]. The Consodilated Standards of Reporting Trails (CONSORT) has been depicted in [Table/Fig-2].

STATISTICAL ANALYSIS

A type I error level of 5% (two-sided) will be regarded statistically significant. Intention-to-treat and per-protocol populations will be used in the analysis. For each group, baseline characteristics were offered, as well as predicting factors. Paired and unpaired t-tests will be performed to assess the data at each time point for comparisons between the experimental and control groups. The univariate analysis is the initial phase. Data with a normal distribution will be analysed using paired and unpaired t-tests. Patients were followed-up at day 0, day 15, day 30, day 45, and day 60. Objective parameters were assessed after completion of treatment, and the data were statistically analysed using descriptive and inferential statistics, the student's paired t-test, and z-proportion test. A p-value of <0.05 is considered statistically significant.

Group	Sample size	Intervention	Dose and frequency	Anupan	Duration	Follow-up
A	30	*Nisha-amalaki* (intervention)	6 gm (twice a day in equal divided doses) [14]	Luke warm water	60 days	On 15th, 30th, 45th and 60th day. No any adverse effects or side effects were observed in any patient. The fasting and PMBS levels and BMI was taken at the start and end of the study.
B	30	Metformin (standard control)	1 gm (twice a day in equal divided doses)	Water	60 days	On 15th, 30th, 45th and 60th day.

[Table/Fig-1]: Grouping and posology.
*As per the systematic review conducted honey by Akhbari M et al., [15] Luke warm water was taken as Anupan in place of honey [14,15]



[Table/Fig-2]: CONSORT flowchart.

RESULTS

The age-wise distribution of subjects in both groups is provided in [Table/Fig-3]. Out of 60 subjects, 33 (55.4%) were aged between 51-60 years, 23 (38.3%) were aged between 41-50 years, and 4 (6.7%) were aged between 31-40 years. The gender-wise distribution of subjects in both groups is detailed in [Table/Fig-4]. In present study, the gender wise distribution showed that out of 60 subjects, 33 (55.0%) were males, and 27 (45.0%) were females.

Group	Age (in years), n (%)			
	31-40	41-50	51-60	Total
Metformin (Group M)	2 (6.7%)	9 (30.0%)	19 (63.3%)	30 (100%)
Nisha-amalaki (Group N)	2 (6.7%)	14 (46.66%)	14 (46.66%)	30 (100%)
Total	4 (6.7%)	23 (38.3%)	33 (55.4%)	60 (100%)

[Table/Fig-3]: Age-wise distribution of subjects in both groups.

Group	Gender, n (%)		
	Male	Female	Total
Metformin (Group M)	18 (60.0%)	12 (40.0%)	30 (100%)
Nisha-amalaki (Group N)	15 (50.0%)	15 (50.0%)	30 (100%)
Total	33 (55.0%)	27 (45.0%)	60(100%)

[Table/Fig-4]: Gender-wise distribution of subjects in both groups.

The distribution of subjects according to the exercise pattern in both groups is mentioned [Table/Fig-5]. It was observed that out of 60 subjects, 47 (78.3%) were not exercising at all, and 13 (21.7%) were exercising regularly.

Group	Excercise, n (%)		
	Regular	No	Total
Metformin (Group M)	7 (23.3%)	23 (76.6%)	30 (100%)
Nisha-amalaki (Group N)	6 (20.0%)	24 (80.0%)	30 (100%)
Total	13 (21.7%)	47 (78.3%)	60 (100%)

[Table/Fig-5]: Distribution of subjects according to their exercise in both groups.

The comparison of mean FBS level before and after treatment in both groups is mentioned [Table/Fig-6]. In Group M, the mean FBS level before treatment was 151.98±27.442 mg/dL, which significantly reduced to 138.56±24.948 mg/dL after treatment with t and p-values of (2.801, p=0.009, S). In Group N, the mean FBS level before treatment was 143.08±24.646 mg/dL, which reduced to 129.39±27.173 mg/dL after treatment, and this reduction was statistically significant with t and p-values of (2.854, p=0.008, S).

When comparing both groups using the Z-proportion test, the z-value was -1.084, and the p-value was 0.280, indicating a non significant difference in the % change of FBS, suggesting that both groups are equally effective in reducing FBS levels.

The comparison of mean PMBS level before and after treatment in both groups is detailed in [Table/Fig-7].

Groups	Mean±SD FBS (BT)	Mean±SD FBS (AT)	% change	Paired t Statistic	Z proportion test	p-value (intergroup)	p-value (intragroup)
Metformin (Group M)	151.98±27.442	138.56±24.948	8.83%	2.801	-1.084	0.009*	0.280 Non significant difference in % change of FBS
Nisha-amalaki (Group N)	143.08±24.646	129.39±27.173	9.57%	2.854		0.008*	

[Table/Fig-6]: Comparison of Mean Fasting Blood Sugar (FBS) level before and after treatment in both groups.
*Significant difference at 5% level of significance

Group	Mean±SD PMBS (BT)	Mean±SD PMBS (AT)	% change	Paired t Statistic	Z proportion test	p-value (intergroup)	p-value (intragroup)
Metformin (Group M)	232.45±41.609	230.35±46.022	8.83%	0.291	-4.155	0.773	0.001 Significant difference in % change of PMBS
Nisha-amalaki (Group N)	223.56±51.838	209.26±57.886	9.57%	1.729		0.094	

[Table/Fig-7]: Comparison of mean Post Meal Blood Sugar (PMBS) before and after treatment in both groups.

In Group M, the mean PMBS level before treatment was 232.45±41.609, which reduced to 230.35±46.022 after treatment; this change was statistically non significant with t and p-values of (0.291, p=0.773, S). In Group N, the mean PMBS level before treatment was 223.56±51.838, which reduced to 209.26±57.886 after treatment; this reduction was also statistically non significant with t and p-values of (1.729, p=0.094, S).

When comparing both groups using the Z-proportion test, the z-value was -4.155, and the p-value was 0.001, indicating a significant difference in the % change of PMBS. This suggests that *Nisha-amalaki* has a better effect compared to Metformin in reducing PMBS levels.

In Group M, the BMI before treatment was 26.49±0.900, which reduced to 26.23±0.899 after treatment; this change was statistically significant with t and p-values of (15.661, p=0.001, S). In Group N, the BMI before treatment was 26.06±0.826, which reduced to 25.86±0.804 after treatment; this reduction was also statistically significant with t and p-values of (15.314, p=0.001, S).

When comparing both groups using the Z-proportion test, the z-value was 2.459, and the p-value was 0.013, revealing a significant difference in the % change of BMI. This means that Metformin has a better effect compared to *Nisha-amalaki* in reducing BMI [Table/Fig-8].

Groups	Mean±SD BMI (BT)	Mean±SD BMI (AT)	% change	Paired t Statistic	Z proportion test	p-value (intergroup)	p-value (intragroup)
Metformin (Group M)	26.49±0.900	26.23±0.899	0.98%	15.661	2.459	0.001*	0.013 Significant difference in % change of BMI
Nisha-amalaki (Group N)	26.06±0.826	25.86±0.804	0.77%	15.314		0.001*	

[Table/Fig-8]: Comparison of mean Body Mass Index (BMI) before and after treatment in both groups.
*Significant difference at 5% level of significance

DISCUSSION

According to demographic statistics, Diabetes Mellitus is most common in the age group of 51 to 60 years. The percentage of females and males affected by *Madhumeha* is 45% and 55%, respectively. It is worth mentioning that *Madhumeha* can affect individuals of any gender; however, due to their stressful and sedentary lifestyles, males may experience it more frequently. Previous research investigations by Deshpande S et al., and Kundu S et al., have indicated that the incidence of the disease is higher in age groups between 40 and 60 years [16,17]. The present data clearly shows that the condition is common among elderly people. The cause could be attributed to factors such as stress, addiction, poor eating habits, and a sedentary lifestyle [18].

Other research studies [19-22] found a higher prevalence of the disease in males in their studies, revealing that Diabetes was present in 34 individuals (5%; 20 men and 14 women) and impaired glucose tolerance in 15 individuals (2%; eight men and seven women). Thus, a total of 49 individuals (7%) had abnormal glucose tolerance. Total 13 of those with diabetes were receiving treatment. Gender differences arising from psychosocial and cultural processes, such as different behaviours, lifestyles, and attitudes towards prevention and treatment, also impact the susceptibility and progression of Type-2 diabetes.

In present study, 78.3% of patients were found to be suffering from Type-2 Diabetes Mellitus and were not exercising, whereas only 21.7% of patients had a history of regular exercise. This clearly indicates that regular exercise plays a role in the occurrence of Type-2 Diabetes Mellitus. Research conducted by Joseph JJ et al., showed that the incidence of Type-2 Diabetes Mellitus in patients who do not exercise is higher than in those who do regular exercise [23].

The mean FBS level before treatment was 151.98 and 143.08 in Group M and Group N, respectively, which significantly reduced to 138.56 and 129.39 after treatment. This depicts that both *Nisha-amalaki Churna* and Tablet Metformin are equally effective in reducing FBS levels. The mean PMBS level before treatment was 232.45 and 223.56 in Group M and Group N, respectively, which

reduced to 230.35 and 209.26 after treatment. This depicts that *Nisha-amalaki Churna* is more effective than Tablet Metformin in reducing PMBS levels. The mean BMI before treatment was 26.49 and 26.06 in Group M and Group N, respectively, which reduced to 26.23 and 25.86 after treatment. This reveals that Metformin is more effective than *Nisha-amalaki* in reducing BMI.

The animal study conducted by Bedarkar P [24] showed that at dose levels of 90 and 180 mg/kg, *Nishamalaki Churna* (fine powder of *Curcuma longa* and *Emblica officinalis* 1:1) significantly decreased ($p<0.05$-0.01) hyperglycemia compared to the glucose-treated group [25]. When compared to the normal group's animals, the glucose control group's animals displayed a substantial ($p<0.01$) rise in glucose levels following 30 minutes of glucose delivery. *Nishamalaki Churna* has a hypoglycaemic impact comparable to that of regular metformin.

A clinical trial on *Nisha-amalaki* in the management of *Madhumeha* vis-à-vis diabetes mellitus was conducted by Yadav RK [25] revealing that the medication *Nishamalaki* appears to be a risk-free and economical treatment for Diabetes mellitus. It might not be as helpful for people whose FBS levels are higher than 200 mg%. An oral hypoglycaemic medication may be added in such a situation. Due to its superior safety profile, this medication can be used in conjunction with current oral hypoglycaemic medicines as an adjuvant.

A study conducted by Rao G demonstrated that diabetic rats treated with *Nishamalaki* had significantly lower plasma glucose levels than those treated with Troglitazone [26]. In one animal study, *Nisha-amalaki Churna* was also found to be a weight-reducing agent [27]. In a study conducted by Yadav KD, Chaudhary AK, it was revealed that Turmeric has anti-inflammatory and antioxidant properties, boosts adiponectin concentration, and keeps the balance of nutritional components, genetic points, and therefore might be advantageous for the management of obesity [28].

Probable mode of action of *Nisha-amalaki:* *Nisha-amalaki* contains *Haridra (Curcuma longa L)* and *Amalaki (Emblica officinalis Gareth).* In experimental animal models, its rhizomes were shown to exhibit antidiabetic characteristics. Curcumin, the key component, was shown to have antidiabetic properties, according to researchers [29].

Haridra's Veerya (potency) is *Ushna* and has *Tikta Rasa*, both of which are advantageous in *Kaphaja Vikaras*. These drugs have properties like *Ruksha, Ushna, Tikshna*, and *Katu Vipaka* that help with *Samprapti Vighatana* (pathogenesis) and so aid in the treatment of Type-2 Diabetes Mellitus patients [30]. A study conducted by Maithili N et al., revealed that turmeric may be added as an adjuvant to antihyperglycemic medication in order to avoid or delay Type-2 DM molecular consequences. Consequently, turmeric helps to maintain normoglycemic status and prevent the emergence of complications [31]. A study conducted by Zinjarde SS et al., showed that the enzyme Human Pancreatic Amylase (HPA) was most effectively inhibited by the *Curcuma longa* isopropanol and acetone extracts. Less starch hydrolysis due to this HPA suppression reduces blood glucose levels [32].

In a systematic review conducted by Zhang D-W it was studied that most of the main hallmarks of diabetes, including insulin resistance, hyperglycemia, hyperlipidemia, and islet apoptosis and necrosis, may be positively impacted by Curcumin (the main constituent of Turmeric). Curcumin also has the potential to prevent the negative effects of diabetes complications [33]. In a study conducted by Ghorbani Z et al., it was revealed that by decreasing hepatic glucose production and glycogen synthesis and stimulating glucose uptake, Curcumin can lower blood sugar and HbA1c levels. This is accomplished by suppressing hyperglycemia-induced insulin resistance [34].

Ellagic acid in *Emblica officinalis* exhibits antidiabetic effects by stimulating insulin production and decreasing glucose intolerance in diabetic rats. Immunohistochemistry of the pancreas revealed that *Emblica officinalis* boosted Beta cell size and number in diabetic rats. It also increased glucose-stimulated insulin production from isolated islets and reduced glucose intolerance in diabetic rats [35]. *Amalaki (Emblica officinalis)* is mostly composed of alkaloids, phenolic chemicals, amino acids, and carbohydrates. In a study conducted by Muruhananthan G et al., it was revealed that in tests using the Oral Glucose Tolerance Test (OGTT) and herbal preparations made with *Emblica officinalis* extract on normal and diabetic rats, there was a significant, minimal, and very slight decrease in blood glucose levels [36].

As *Madhumeha* is *Kaphjanya Vikar*, due to the *Ushna* and *Tikshna* properties of *Haridra* and *Amalaki*, they act on *Kapha dosha* to decrease it and thereby aid in the management of *Madhumeha* [37].

Limitation(s)

Limitation of the present study was that the Glycosylated Haemoglobin (HbAIC) was not assessed to evaluate the efficacy of the trial drug on sugar control.

CONCLUSION(S)

Madhumeha is more prevalent in the 51-60 years age group, as well as in males compared to females. Patients who do not exercise were found to have more incidence of Type-2 Diabetes Mellitus. Upon comparing both groups, a non significant difference in the % change of FBS suggests that both groups are equally effective in reducing FBS levels. *Nisha-amalaki* has a better effect compared to Metformin in reducing PMBS levels, while Metformin has a better effect compared to *Nisha-amalaki* in reducing BMI. *Nisha-amalaki Churna* is found to be equally effective in overweight and obese diabetic patients. *Nisha-amalaki* (a combination of daily use herbs *Haridra* and *Amalaki*) is effective in normalising blood sugar levels for patients with FBS in the range of 126-200 mg/dL and PMBS in the range of 200-300 mg/dL, with a BMI range of 25-30 kg/m^2.

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