A STUDY ON COMBINED EFFECTS OF TMF-27 AND TMF-35 ON PATIENTS WITH TYPE 2 DIABETES MELLITUS

Win Myint
Associate Professor/ Head
Department of Medicine
University of Traditional Medicine

TITLE

A STUDY ON COMBINED EFFECTS OF TMF-27 AND TMF-35 ON PATIENTS WITH TYPE 2 DIABETES MELLITUS

OBJECTIVES

General Objective

- To study the antihyperglycemic effect of traditional combined drug TMF-27 and TMF-35 on type 2 Diabetes Mellitus patients (madhumeha)

Specific Objectives

- To determine the glycemic status of type 2 diabetes mellitus patients before treatment day 0
- To determine the glycemic status of type 2 diabetes mellitus patients during treatment day 7, day 14 and day 21
- To determine the glycemic status of type 2 diabetes mellitus patients at the end of the study day 28
- To compare the glycemic status of type 2 diabetes mellitus patients at day 0 with those at day 7, day 14, day 21, day 28
- To observe the untoward effects of the combined drug TMF-27 and TMF-35

INTRODUCTION

- Diabetes Mellitus(DM) is one of the most commonly occurring problems round the globe
- WHO, 1999 estimates that by the year 2030, DM patients will have reached 370 million
- WHO estimated that, by 2020 chronic disease will account for almost three quarters of all deaths worldwide,75 % death due to stroke, 71 % death due to ischemic heart disease and 70 % death due to diabetes will occur in developing countries (WHO, 1998)
- WHO estimates that more than 80% of the world's population rely either solely or largely on traditional remedies for healthcare (WHO, 2005)

- Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physician Sushruta and Charaka in 400-500 AD with type 1 associated with youth and type 2 with being overweight
- Plants, their extract or traditional formulae may also have a potential therapeutic role in controlling blood sugar level
- TMF-27 and TMF-35 have been used by Myanmar traditional medicine practitioners for a long time without adverse effect
- This clinical trial was conducted to identify the blood glucose lowering effect of TMF-27 and TMF-35, and to assess the side effect(s), if any, on patients with type 2 DM

Justification

- In Myanmar, Diabetes mellitus (DM) is one of the six leading diseases of morbidity
- Patients with uncomplicated DM are asymptomatic or mildly symptomatic and they only notice that they have DM during medical check up or seeking management for other diseases
- Western antihyperglycemic drugs are expensive and poorly accessed by the people with low socio-economy status
- Myanmar TMF-27 and TMF-35 are popular drugs used in traditional therapy and these are safe, effective and easily accessible in community with low cost

- TMF-27 is predominent in bitter taste, and TMF-35 is predominent in hot pungent taste
- The combined drug which has hot bitter and pungent tastes will be effective for Sangahita group diseases
- Diabetes Mellitus (Madhumeha) is one of the Sangahita diseases
- Combined drug TMF-27 and TMF-35 will have antihyperglycemic effect on the patients with type 2 diabetes mellitus
- This study will provide a new hope for type 2 diabetes mellitus patients especially for poor and those who could not effort to western antihyperglycemic drugs

LITERATURE REVIEW

Diabetes Mellitus in Myanmar Traditional Medicine Literature

သည်းခြေ၊ သလိပ်ကြောင့် ပမေဟရောဂါပင် ဖြစ်သော်လည်း အလုံးစုံသော ပမေဟရောဂါတို့သည် ဆေးမကုသော သူတို့အားအချိန်ကြာလျှင် မဓုမေဟ(ဆီးချို) အဖြစ်သို့ရောက်သွား၏ မဓုမေဟဖြစ်သွားလျှင် အသာချဖြစ်၏ ။ မဓုမေဟရောဂါစွဲကပ်သောသူ၏ ဆီးသည်ပျားရည်နှင့်တူပြီး ချိုသောအရသာ ရှိ၏ ထိုမဓုမေဟရောဂါသည် နှစ်မျိုးရှိ၏ (၁) ဓါတ်ကုန်ခမ်းပြီး လေပျက်သောကြောင့် တစ်မျိုးဖြစ်ခြင်း။ (၂) သည်းခြေစသော ဒေါသတို့ကြောင့် လေလမ်းပိတ်ဆို့ပြီး လေလမ်းဖုံးလွှမ်း သောကြောင့် ဖြစ်ခြင်း။ နှစ်မျိုးရှိ၏ (လှတင်(ဦး) သျှရိန့် ဆရာမှီ (သမားတော်ကြီး)၊ ၁၃၂၅ ခုနှစ်)။

- If it is not treated properly, the Prameha due to Pitta, Kapha leads to Madhumeha which is incurable

- The taste of urine of Madhumeha patient is sweet and like honey. There are two types of Madhumeha as follow:

1. Vata vitiation due to depletion of body tissue (Dhatu)
2. The obstruction of Vata Srota due to destructed Dosha (Pitta, Kaph etc.)

Diabetes Mellitus in Ayurveda

-Ten different types of urine have been described in Khapha type “Prameha”:

-Six different types of urine have been described in Pitta type “Prameha”:

- Four different types of urine have been described in Vata type “Prameha”:

Madhumeha- Is one of the Vata type disease of Prameha”

Diabetes Mellitus (Madhumeha)in Desana Medicine

Madhumeha is occured by the following factors:

1. Excessive eating of cool, sweet , astringnent and fatty diets (ahara)
2. Exposure to cold season and regions (Utu)
3. Absence of physical exercise (present kamma)
4. Failure of Parchakagni (Digestive disorder) and Dhatwagni (Disorder of hormone secretion)
5. Genetic factors (past kamma)

- The main treatment tastes were hot bitter and pungent
- The drugs which had hot bitter and pungent tastes were useful for DM
- TMF-27 and TMF-35 would have antihyperglycemic effect on patients with type 2 DM

Table 1. Diabetes diagnostic criteria

Condition	**2 hour glucose**	**Fasting glucose**	**HbA_{1c}**
	mmol/l(mg/dl)	mmol/l(mg/dl)	%
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥6.5

(Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia report of a WHO/IDF consultation)

TMF-27 and Composed Medicinal Plants

- TMF-27 is traditionally used for the treatment of the paralysis (Hemiplegia) for many years ago
- TMF-27, Pyilonechanthar Hasay is composed of 16 medicinal plants
- *Tinospora* sp (stem) is the major ingredient of the formulation. One third of the drug is composed of Hsindonmanwei . (Department of Medical Research, 1989)

Scientific name	**Myanmar name**	**amount in g/100 g**
1)*Tinospora cordifolia* Miers (stem)	Sin done ma nwe	33.45
2)*Cassia renigera* Wall (root)	Phwar bat gyi	4.46
3)*Clerodendrum phlomoides* Linn	Ta pa say	4.46
4)*Croton oblongifolius* Muell (root)	Thet yin gyi	4.46
5)*Dragea volubilis* Benth (root)	Gway dauk myit	4.461

Scientific name	Myanmar name	amount in g/100 g
6)*Holarrhena antidysenterica* Wall(root)	Let htoke gyi	4.46
7)Jatropha multifida Linn (stem)	say ma khan	4.46
8)*Oroxylum indicum vent* (bark)	Kyaung shar khauk	4.46
9)*Millettia glaucescens* (stem)	Thin win pauk phyu	4.46
10)Strychnos *potatorum* Linn (root)	Kha baung ye kyi	4.46
11)*Plumbago rosea* Linn (root)	Kant choke ni	4.46
12)*Carallia brachiata* Merr (bark)	Mani au ga	4.46
13)*Tarennoidea wallichii* (bark)	Kat ma	4.46
14)*Strychnos nux-vomica* Linn (root)	Kha baung gyi	4.46
15)Gentiana *kurroo* Royle (root)	Say pa le	4.46
16)*Artabotrys burmanicus* A.Dc (stem)	Nga pyay yin	4.46

TMF-35 and Composed Medicinal Plants

- TMF-35 is traditionally used for the treatment of fever for many years ago. The formulation contains 23 items of herbal plants,

Scientific name	Myanmar name	amount in g/100 g
1)*Myristica fragrans* Houtt	Zar deik pho thee	4.35
2)*Foeniculum vulgare* Mill	Samon sabah	4.1
3)*Trachyspermum ammi* Linn	Samon phyu	4.1
4)*Anethum sowa* Roxb	Samon nyo	4.1
5)*Foeniculum vulgare* Linn	Samon phwe	4.1
6) *Lepidium sativum* Linn	Samon ni	4.1

Scientific name	Myanmar name	amount in g/100g
7) *Sausscerea* sp.	Pannu	4.1
8) *Anneslea fragrans* Wall	Panma	4.1
9) *Terminalia chebula* Retz	Katara thin che	4.1
10) *Oldenlandia corymbosal*	Sular na phar	4.1
11) *Picorhiza kurroa* Royle	Saung may khar	4.1
12) *Cuminum cyminum* Linn	Ziyar	4.1
13) *Cinnamomum inunctum* Meissn	Kara way ywet	4.1
14) *Mesua ferrea* Linn	Gant gaw wut san	4.1
15) *Piper nigrum* Linn	Nga yoke kaung	4.1

Scientific name	**Myanmar name**	**amount in g/100 g**
16) *Piper longum* Linn	Peik chin thee	4.1
17)*Zingiber officinale* Roscoe	Gyin chauk	4.1
18)*Cinnamomum zeylanicum* Nees	Thit gya bo	4.1
19)*Elettaria cardamomun*	Pharlar nge	4.1
20)*Plumbago rosea* Linn	Kant choke ni	4.1
21)*Hemidesmus indicus* R.Br	U Pa tha ka	4.1
22)*Terminalia citrina* Roxb	Kyazoot	4.1
23)*Syzygium aromaticum* Linn	Lay hnyin	4.1

Toxicity of TMF-27

- Not toxic on acute administration (where the maximum LD_{50} limits on mice, rats and rabbits being greater than 4.8, 2.4 and 1.2 gm/kg respectively) (Department of Medical Research,1989)

Toxicity of TMF-35

- Not toxic on acute administration (where the maximum LD_{50} limits on mice, rats and rabbits being greater than 3.2, 1.6 and 0.8 g/kg respectively) (Department of Medical Research, 1989)

RESEARCH METHODOLOGY

1. Study Design

- Hospital based therapeutic trial

2. Study Site

- Medical ward, (100) Bedded Traditional Medicine Teaching Hospital, Mandalay

3. Study Population

- Type 2 Diabetes Mellitus patients admitted to Medical ward, Traditional Medicine Teaching Hospital, Mandalay

4. Selection Criteria

4.1 Inclusion criteria

Subjects were selected according to WHO definition.

- Type 2 Diabetes Mellitus patients (with DM signs and symptoms) and fasting blood sugar (FBS) ≥ 126 mg/dl
- Random blood sugar (RBS) ≥ 200 mg/dl.

Sex	-	both sexes
Age	-	35 – 60 years

4.2 Exclusion criteria

- Pregnant or lactating mothers
- Those receiving corticosteroid therapy
- Severe complications of Diabetes Mellitus
- Hypertension more than 160/95 mmHg
- History of bleeding tendency
- Subject's request
- Patient developing hypoglycemic shock or hyperglycemia
- FBS $\leq$ 63 mg/dl (3.5 m mole/l) for hypoglycemia
- FBS $\geq$ 500 mg/dl (27.78 m mole/l) for hyperglycemia
- Attending physician's recommendation because of side effects

5. Study Period

- The study will be carried out from 1st April 2012 to 30th October 2012.

6. Sample Size Calculation

- Confidence interval - 95%
- Power - 80%
- Treatment effect - 50% reduction
- Required Sample - 34
- Epi Info version - 3.4.1

7.Materials and Methods

Material used :

- Test drug (Natural powder of combined TMF-27 and TMF-35) 8 kg (4 kilos for each)
- Combination method – Natural powder of TMF-27 and TMF-35 are combined equally in weight

  -The mixed powder drug of TMF-27 and TMF-35 are transformed to tablets of 1gm weight

  -The patient has to take four tablets (4 gm) three times per day
- 3cc sterilized syringes and needles (to take venous blood)
- Collection tubes (30×5) = 150 tubes.
- Sphygmomanometer (mercury type)

- After taking recruitment FBS of the subject was measured
- After an over night fast, about 3.cc of venous blood was taken from brachial vein by using sterilized and disposable needle and syringe in the next morning six o'clock
- The blood sample was collected in collection tube and sent to laboratory technologist in TMTH, Mandalay to determine the glucose level
- The subject was given combined drug TMF-27 and TMF-35 (4g) 3times per day for 7 days and FBS and 2-hour post prandial (2 HPP) blood sugar (day 7) were measured at respective point
- After reviewing the results, all subjects were provided with diet control and regular physical activity advice for the control of their blood sugar level and any adverse effects of drug were observed

- This procedure was repeated during each of the 3 successive times (on day 14, day 21 and day 28), respectively. Then glucose levels were measured and any adverse effects were under taken
- Signs and symptoms of hypoglycemia and hyperglycemia were observed
- When hypoglycemic or hyperglycemic signs and symptoms appeared, necessary treatment will be given immediately
- In case of emergency, assigned Medical Officer has to inform to Physician and to try (well – planned schedule prior to trial) as soon as possible after giving emergency care for hypoglycemia or hyperglycemia

8.Data Processing and Analysis

- Fasting blood sugar level, biochemical parameters had recorded and statistical analysis had done
- If the FBS levels were equal or greater than 126 mg/dl, the patient was diagnosed as Diabetes Mellitus type 2
- Then he/she was selected for the trial and was explained about the research and obtained inform to participate the study
- After taking the consent form, the subjects were measured body weight, height, blood pressure, total cholesterol levels test as a base line data

- After three days later (for washing out period) FBS levels of subjects were measured before treatment day 0 and recorded.
- FBS measurement was taken about six times on day 0, day 7, day 14, day 21 and day 28. Two hour post prandial (2HPP) blood sugar levels were taken only on day 7. Then FBS data were saved systematically and data analysis were done.
- During the experimental period the subjects were controlled for their diet

Statistical analysis

- The data were presented as mean ± SD
- Changes in FBS were analyzed by ANOVA of repeated measures; changes between weeks of medication and safety measures were analyzed using paired t test for pre and post trial
- The significance level was set at $p < 0.05$
- The collected data were shown in table 2

No.	Age	FBS mg/dl day 0	FBS mg/dl day 7	FBS mg/dl day 14	FBS mg/dl day 21	FBS mg/dl day 28	2HPP mg/dl day 7
1	60	252	257	257	180	214	428
2	58	396	216	270	234	180	450
3	57	324	216	270	223	217	360
4	60	252	189	237	194	154	360
5	59	364	372	207	234	242	457
6	59	196	221	187	183	212	338
7	45	234	171	133	121	158	291
8	39	171	151	140	132	127	361
9	35	259	145	133	158	136	217
10	60	165	120	117	113	110	215
11	59	156	138	136	131	145	226

12	58	331	170	148	140	110	184
13	60	156	109	129	102	108	122
14	60	318	183	193	226	207	252
15	54	518	447	484	320	230	502
16	60	280	200	180	155	126	252
17	57	127	120	127	120	125	138
18	55	397	183	156	130	122	273
19	59	211	103	142	120	120	139
20	60	128	100	129	120	118	192
21	56	335	198	229	180	130	345
22	48	282	304	240	180	125	583
23	58	127	130	120	126	110	189
24	60	135	120	97	132	112	140

25	58	129	129	68	104	83	138
26	60	140	130	130	125	120	180
27	60	127	156	120	118	120	172
28	49	136	140	130	133	125	200
29	52	252	156	144	130	125	297
30	52	500	479	164	258	216	498
31	35	129	115	108	116	112	185
32	50	186	155	140	144	125	188
33	60	235	157	125	147	114	198
34	43	442	252	295	387	270	529

Table 2. FBS Data collection of subjects with DM type 2

ETHICAL CONSIDERATION

- The study was approved by the Institutional Ethical Review Committee of University of Traditional Medicine, Mandalay
- All procedure made in this study were free of charge
- Participation in this research work was on the subject's own desire without being persuaded or threatened
- The subjects were free to withdraw from the study at any time according to the subject's desire

RESULTS

- The collected data were analyzed by paired " t " test and ANOVA.
- Table 3. Mean Score of FBS levels before and after 7 days of treatment

	Paired Differences					t	df	Sig(2-tailed)
	Mean	SD	SE	Mean Score				
				Day 0	Day 7			
Day0-Day7	57.588	66.34	11.37	246.76	189.18	5.062	33	0.000

p-value = 0.0001<0.05

This table showed FBS reduction of the subjects after one week medication. Mean Score of FBS levels reduced from 246.76 (day 0) to 189.18 (day 7). Standard deviation was 66.34 and p-value was 0.0001. Therefore the treatment was significant statistically.

Table 4. Mean Score of FBS levels before and after 14 days of treatment

	Paired Differences					t	df	Sig(2-tailed)
	Mean	SD	SE	Mean Score				
				Day 0	Day 14			
Day0-Day14	73.676	76.281	13.082	246.76	173.09	5.632	33	0.000

p-value = 0.0001<0.05

•This table showed FBS reduction of the subjects after two weeks medication. Mean Score of FBS levels reduced from 246.76 (day 0) to 173.09.18 (day14).Standard deviation was 76.281 and p-value was 0.0001. Therefore the treatment was significant.

Table 5. Mean Score of FBS levels before and after 21 days of treatment

	Paired Differences					t	df	Sig(2-tailed)
	Mean	SD	SE	Mean Score				
				Day 0	Day 21			
Day0-Day21	81.588	71.235	12.217	246.76	165.18	6.678	33	0.000

p-value = 0.0001<0.05

This table showed FBS reduction of the subjects after three weeks medication. Mean Score of FBS levels reduced from 246.76 (day 0) to 165.18 (day 21). Standard deviation was 71.235 and p-value was 0.0001. Therefore the treatment was significant.

Table 6. Mean Score of FBS level before and after 28 days of treatment

	Paired Differences					t	df	Sig(2-tailed)
	Mean	SD	SE	Mean Score				
				Day 0	Day 28			
Day0-Day28	98.294	87.233	14.960	246.76	148.47	6.570	33	0.000

p-value = 0.0001<0.05

These tables showed significant of treatment. Mean FBS level of before treatment was 246.76 and after 28 days of treatment was 148.47 and " p " value was < 0.0001. The effect of combined drug TMF-27 and TMF-35 was significant on DM type 2 patients in this study after 28 days treatment.

Table 7. Mean FBS scores on day7, day 14, day 21 and day 28

Groups	*Count*	*Sum*	*Average*	*Variance*
FBS day 7	34	6432	189.1765	8308.756
FBS day 14	34	5885	173.0882	6130.75
FBS day 21	34	5616	165.1765	4087.483
FBS day 28	34	5048	148.4706	2266.499

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between groups	29235.85	3	9745.282	1.87468	**0.136959**	2.673218
Within Groups	686185.1	132	5198.372			
Total	715420.9	135				

- The difference in FBS values between day 7 and day14, day 14 and day 21, day 21 and day 28 was not significant ($p>0.05$)
- These was gradual lowering of FBS for day 7 to day28.

Table 8. Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
FBS day 0	34	8390	246.7647	12747.94
FBS day 7	34	6432	189.1765	8308.756
FBS day 14	34	5885	173.0882	6130.75
FBS day 21	34	5616	165.1765	4087.483
FBS day 28	34	5048	148.4706	2266.499

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	193817.1	4	48454.27	7.223048	2E-05	2.426438
Within Groups	1106867	165	6708.286			
Total	1300684	169				

p-value = 0.00002 < 0.05

This tables showed reduction of FBS level was significant after one week treatment. But, in coming week of study, the lowering of FBS levels were gradually reduced (day 14, day 21 and day 28)

“ P ” value is (0.00002). So, “ p ” value is less than 0.05. Therefore the total reduction of FBS levels from day 0 to day 28 were significantly reduced.

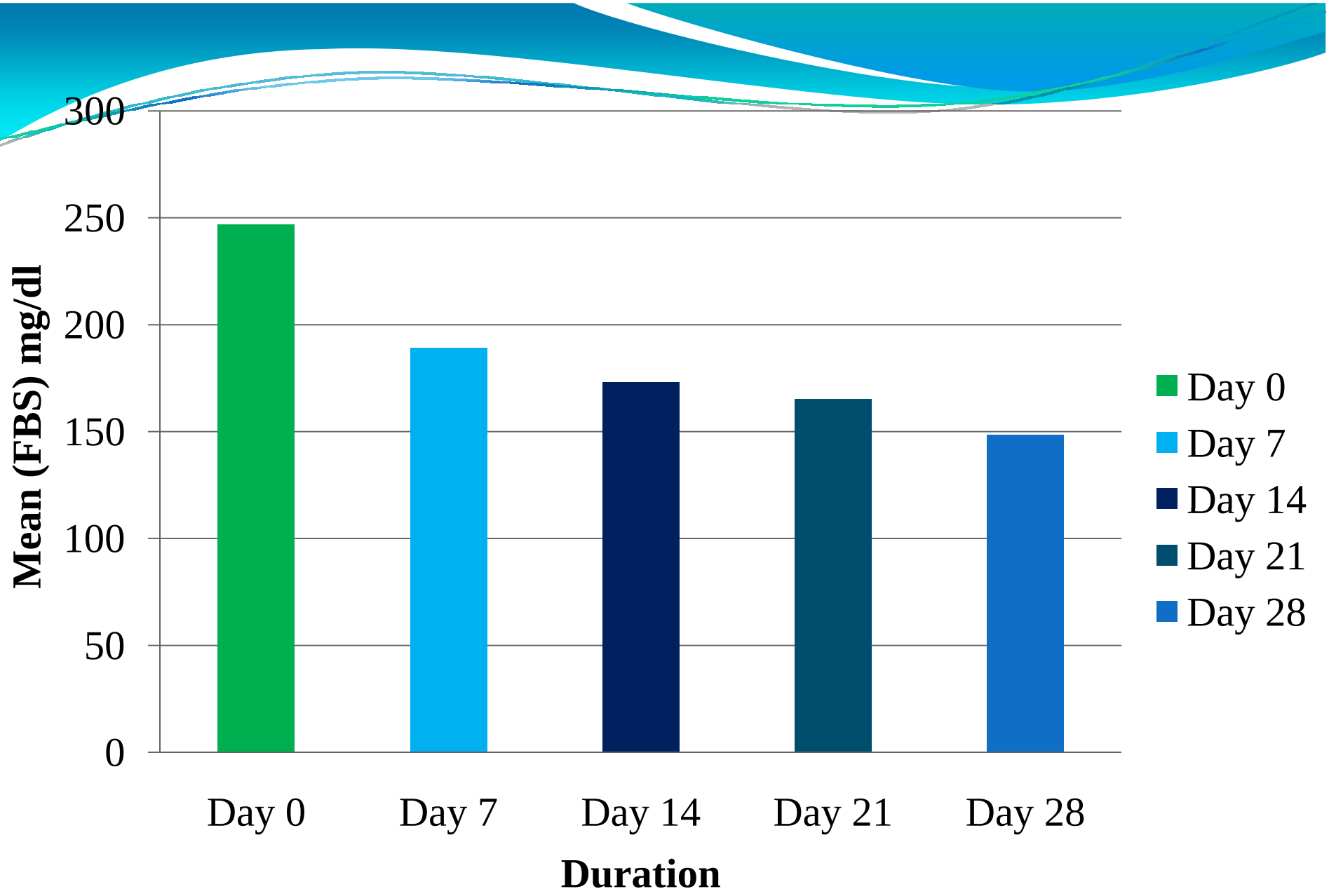

Figure 1. Mean values of FBS for day 0 to day 28

DISCUSSION

Table 9. Age distribution of the subjects

Year	Number of Patients	Minimum	Maximum	Mean	Std.Deviation
Age	34	35	60	54.56	7.399

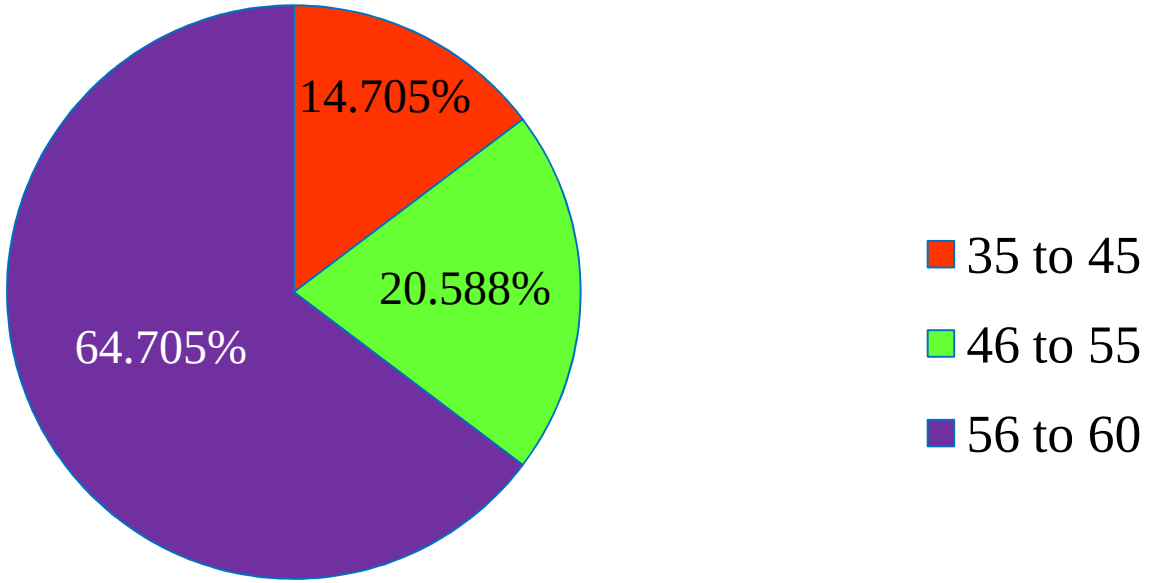

Figure 2. Age group distribution of patients

No	Age year	Number of Patients	Total FBS mg/dll day (0)	Mean FBS mg/dll day (0)	Total FBS mg/dll day (28)	Mean FBS mg/dll day (28)	Reduction %
1	35-45	5	1235	247	803	161	34.8
2	46-55	7	2271	324	1068	153	52.7
3	56-60	22	4884	222	3177	144	35.1

Table 10. Reduction of FBS in age groups

This table showed that the middle age patients between 46 to 55 years had more response to treatment.

Table 11. Reduction of FBS in sex groups

Sr.	Sex	Number of Subjects	MeanFBS mg/dl Day0	MeanFBS mg/dl Day28	Reduction %	Remark
1.	Male	13	239.07	143.69	39.83	
2.	Female	21	251.52	151.43	39.79	

➢Antihyperglycemic reduction effect of combined drug TMF-27 and TMF-35 was found no difference between male and female subjects with DM type 2.

Table 12. Decrease of symptoms on DM patients

No	Symptoms	Number of patients	Percentage(%)
1.	Polyuria	34	100
2.	Polydipsia (Thirst)	34	100
3.	Polyphagia	11	32.35
4.	Itchiness	10	29.41
5.	Peripheral neuropathy	9	26.47
6.	Blurred vision	2	5.88
7.	Vaginal infection	-	-

- The symptoms of polyuria and polydipsia were recovered in 10 subjects after one week medication
- Above these two symptoms were covered in 14 subjects after two weeks, 17 subjects after three weeks and 22 subjects after four weeks respectively
- These two symptoms were still remained in 12 subjects at the end of study
- Other symptoms like polyphagia, itchiness, peripheral neuropathy and blurred vision were not found in concerned patients after treatment of this study.

Table 13. FBS reduction in BMI groups

No	BMI Score	Number of Patients	FBS mg/dl Day 0	FBS mg/dl Day 28	FBS reduction %
1.	< 25	16	267	164	38.5
2.	Pre obese (25 to 29.9)	11	165	93	43.6
3.	Obese Class I (30 to 34.99)	7	92	59	35.8

CONCLUSION

1) Combined drug TMF-27 and TMF-35 had significantly anti-hyperglycemic effect on type 2 Diabetes Mellitus patients
2) Antihyperglycemic effect of combined drug TMF-27 and TMF-35 was significantly reduced after one week medication day 7
3) Antihyperglycemic effect of combined drug TMF-27 and TMF-35 was gradually reduced after 2, 3and 4 weeks medication day 14, 21 and 28
4) There were no any untoward or adverse effects of combined drug TMF-27 and TMF-35 on DM type 2 patients during trial period

5. According to Desana medicine, Madhumeha was a disease of Sangahita
6. Hot bitter and pungent tastes were suitable for Madhumeha TMF-27 and TMF-35 had hot bitter and pungent tastes
7. According to the result of the trial, the combined drug TMF-27 and TMF-35 had antiglycemic effect
8. Therefore antihyperglycemic effect of test drug was significant on patients with type 2 DM

REFERENCE

- လှတင် (ဦး) သျှရိန့် ဆရာမှီ (သမားတော်ကြီး) ။ (၁၃၂၅ - ခုနှစ်) ။ မာဓဂနိဒါန်းဆေးကျမ်းကြီး ။ ဒုတိယအုပ် ဇမ္ဗူမိတ်ဆွေ ။ ပိဋကတ် ပုံနှိပ်တိုက် ။ ရန်ကုန်မြို့ ။
- Abdoderin, *et al.* (2001). *Life course perspective on coronary heart disease, stroke and diabetes:* Key issue and implication for policy and research. World Health Organization, Geneva.
- American Diabetes Association .(January 2010). "Diagnosis and classification of diabetes mellitus". *Diabetes Care* 33: S62–69.
- American Diabetes Association .(January 2012). "Diagnosis and classification of diabetes mellitus". *Diabetes Care* 35: S64–71.
- Carolyn Hannan, (2008). *Moving forward on women, gender equality and diabetes*. United Nations Department of Economic and Social Affair, New York.

- Carvalho EN, Carvalho NA, Ferretra LM. (2003). *Experimental model of induction of diabetes mellitus in rats*. Acta Cir Bras.18 :142-148.
- Department Medical research (Lower Myanmar), (1989). *Catalogue of the Crude Drug Museum*. Pharmacology Research Division, Yangon.
- Department of Medical research (Lower Myanmar), (1989). *Myanmar Traditional Medicine Formulary*. Pharmacology Research Division, Yangon.
- Elsevier/Saunders. (12th ed.). *Williams textbook of endocrinology.* Pg. 1371–1435.
- Frier, B.m & Fisher, M, 2006, Davidson's principles and practice of medicine 20th Edition,Churchill Livingstone, Elseyier.
- International Expert, Committee (2009). "International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes". *Diabetes Care* **32** (7): 1327–34.

- Khin Phyu Phyu, (2009). *Prevalence and risk factors of diabetes mellitus among middleaged school teachers in Mandalay City*. Paper presented at Myanmar Health Research Congress, Yangon.
- Leonid Poretsky, (2009). *Principles of diabetes mellitus* (2nd ed.). New York: USA.
- National Seminar on Medicine Plants and Traditional Medical knowledge, 1999, Gyjarat Ayurved University Jamnagar. India.
- Pinn G.(2003).*Herbal Medicine* , Blackwell Publication Pty Ltd. Tokyo.Japan.
- Ranad Subhash ,Ranade Sunanda and Paranjape MH. (1999). *Ayurvedic Treatment of common disease*, Sirsatgura publication. India Book Centre. Delhi. India.

- The Work Health Report. (1998).*Life in the 21st century*: a vision for all. Geneva. Vijan S (2010).Type 2 diabetes. *Annuals of internal medicine* :5:152-155.
- World Health Organization. (2005). *Operational guidance. Information needed to support clinical trials of herbal products*. Geneva.
- World Health Organizatin. (2006*). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation*. Geneva.
- World Health Organizatin. (2006*). Definition and diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1. Diagnosis and classification of diabetes mellitus*. Geneva.

Thank You!