European Review for Medical and Pharmacological Sciences 2022; 26: 6290-6299

Comparative analysis between mono approach and multi approaches in managing T2DM: a survey-based study

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Abstract. – OBJECTIVE: The aim of the study was to analytically compare the therapeutic effect of the addition of diet modification and regular exercise to oral agents.

MATERIALS AND METHODS: This cross-sectional study surveyed 1248 participants via online and offline modes by employing a questionnaire about an individual's management of diabetes. Group 1 patients follow Single Approach Management for Type 2 Diabetes Mellitus (T2DM), while Group 2 and Group 3 patients follow Multi-Approach Management for T2DM. Based on the answers, the participants were classified into three groups. The diagnostic criteria of Diabetes Mellitus Type-2 in this study were done by determining morning Fasting Blood Sugar (FBS) and glycated Hemoglobin (HbA1c).

RESULTS: The current study found 656 single oral agent users and 592 combination regimens users among all the study participants. The study also found that, among all participants, 511 patients were on mild to moderate diet modification while 325 patients were on moderate to severe diet modification. The study also noted that 232 males and 215 females took Complementary and Alternative Medicines (CAM). Of 447 patients, 12 showed menstrual abnormalities (2.6%), and 18 had mild diarrhoea (4%). The study also found that there is a vital significance of lowering FBS and HbA1c with the management strategies (p=0.000). The study showed a strong association between group 3 and improved FBS and HbA1c (p=0.000).

CONCLUSIONS: This study reveals that diet modification and regular exercise improve FBS and HbA1c levels significantly. Hence, diet modification and exercise can be added as adjuvants and should be incorporated into the management guidelines of T2DM.

Key Words:
FBS, HbA1c, Diabetes, Management, Oral agents, Diet, Exercise.

Introduction

Diabetes Mellitus is a metabolic, multifactorial chronic condition induced by genetic and environmental factors. This metabolic defect occurs in the biochemical mechanism of lipids, carbohydrates and proteins[1]. The primary pathological change that occurs in Type 2 diabetes is insulin resistance. In T2DM, there is increased demand for insulin which cannot be

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sufficiently produced and supplied by pancreatic B cells while in type 1 diabetes mellitus, there is a lack of insulin-producing beta cells and which be managed by replacement of insulin exogenously[2,3].

According to American Diabetes Association (ADA), diabetes is classified into Type 1, Type 2, and gestational diabetes mellitus (GDM). Globally, T2DM is almost 8.3%, and there are more males (198 million) than females (184 million)[4,5]. It has been found that the number of patients with T2DM is expected to increase to about 600 million by 2035, with more than 10% prevalence worldwide. Several reports also mentioned that there are almost 180 million cases go undiagnosed. With a prevalence of 10.9%, the Middle East and North African countries show the highest prevalence globally[6]. Obesity is one of the primary reasons for this high prevalence, and screening of overweight children is one of the most important public measures, as recommended by ADA[7]. Although the detailed genetic mechanism of T2DM is yet to be explored, few crucial conclusions have been drawn to date. About 4%-5% of non-autoimmune diabetes may be monogenic aetiology, popularly MODY (Monogenic Diabetes of the Young). T2DM is not located in one region; instead, the genetic component of T2DM is contributed from many different regions of the genome. In the first half of 2000, gene linkage revealed two genes, namely, calpain 10 (CAPN10) and transcription factor 7-like 2 (TCF7L2), which were found to have an etiological association with T2DM[8,9].

CAPN10 and TCF7L2

This gene belongs to the family known as "calpain" and encodes a cysteine protease. This family of genes plays a role in intracellular remodeling, post-receptor signaling, and other functions related to intracellular mechanisms. In 1996, linkage analysis revealed that a locus on chromosome 2 is an associative factor in causing T2DM and following large meta-analyses have confirmed the association with T2DM occurrences[10,11]. Recent studies have confirmed associations between T2DM with few SNP or Single-Nucleotide Polymorphisms in the TCF7L2 gene[12]. In a few years, the identification of genes associated with T2DM has increased to near about 70. Some of them are Insulin Receptor Substrate 1 (IRS1), Peroxisome Proliferator-Activated Receptor Gamma (PPARG), Potassium Inwardly-Rectifying Channel genes under subfamily J, member 11 (KCNJ11), HNF1 homeobox A (HNF1A), Wolfram Syndrome 1 (wolframin) (WFS1), HNF1 Homeobox B (HNF1B) and HNF4A, TP53, RAPGEF1[12,13].

Several pathophysiologic mechanisms have been linked to T2DM, one of which is decreased glucose re-uptake at peripheral sites like muscles during simultaneous glucose production. This is one pathological feature of insulin resistance. Other pathophysiological mechanisms that play a role in causing T2DM are the elevated level of Free Fatty Acid level, impairment of pancreatic beta cells, and increased lipolysis due to the unavailability of glucose[14]. Recent studies also revealed that insulin resistance is also backed by the presence of adipocytes and non-alcoholic fatty liver, which is also considered the integral pathological state of insulin resistance[15]. It has been found that the abnormality in the functioning of pancreatic beta cells is resulted due to the chronic presence of nutrient-toxicity[16]. Figure 1 shows the inter-relations of the pathophysiological mechanism of T2DM.

Management

Due to high incidence and prevalence, there have been extensive research and studies at different levels, including research sponsored by international collaborations. Several oral agents have been introduced. Apart from oral agents, many institutions have emphasized the holistic approach to management, which includes lifestyle modifications[17].

Several oral agents have been in use for years. One of the most often used is metformin, whose pharmacological mechanism of action intervenes with the gut microbiota and activates AMP-induced protein kinase, leading to inhibition of gluconeogenesis from lactate[18-20]. Sulfonylureas (popularly known as insulin secretagogues) function by increasing insulin secretion by regulating ATP-sensitive potassium channels and the glucose-lowering ability of Sulfonylureas is the most effective, which can lead to the reduction of HbA1c by 1% to 1.5%[17,21,22]. Again, alpha-glucosidase inhibitors were long introduced and used for 20 years, a class of drugs that has more affinity towards binding with brush border epithelium of the intestine and hence, inhibits active absorption and digestion of carbohydrates. This results in lowering postprandial hyperglycaemia. Therefore, Alpha-glucosidase inhibitors do not affect insulin production or secretion. Instead, they regulate carbohydrate digestion and absorption[23,24].

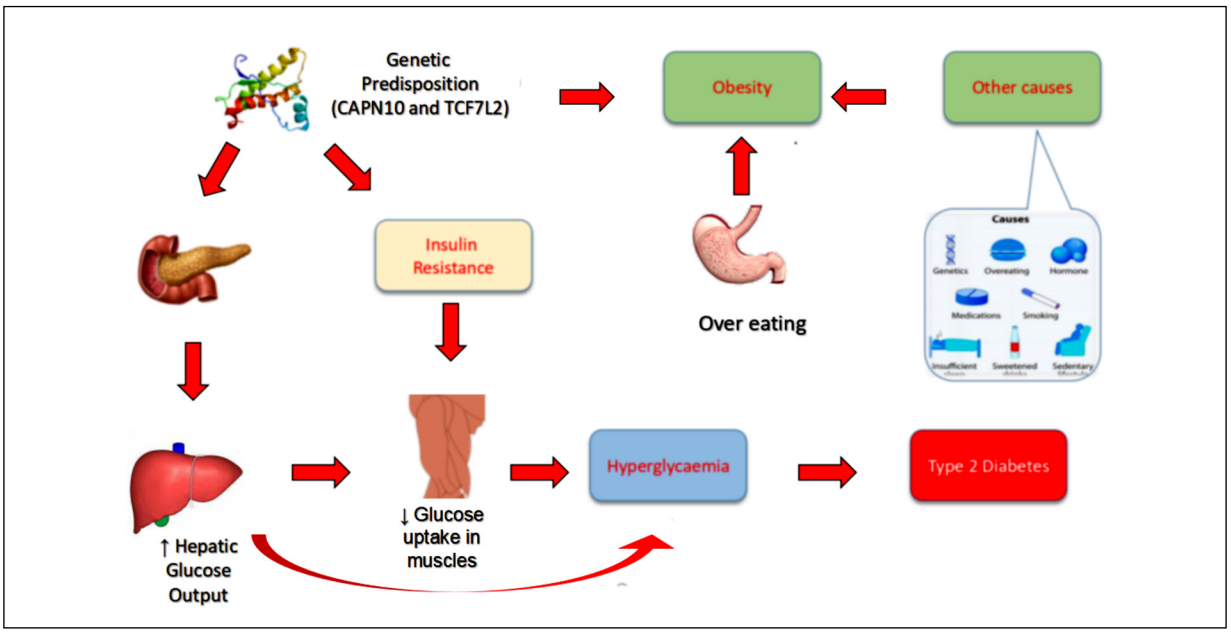

Figure 1. Inter-related pathophysiological mechanism of Type-2 DM.

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) increase the secretion of insulin and causes inhibition of glucagon secretion. DPP-4 inhibitors are said to positively affect pancreatic islet function and regulate glycaemic control efficiently[25]. Table I shows the summary of drug classes available for T2DM management and their respective mechanism.

Materials and Methods

Study Participants

This study is a survey-based cross-sectional study that employed a questionnaire about an individual's management of diabetes. The questionnaire was distributed online as well as offline mode. The online mode included sending emails to the desired participants and sharing the link of the questionnaire via social media platforms and through blog surveys. The offline mode included surveying among friends and family, neighborhoods, etc. The questionnaire did not collect any individual's identity, including name. The study considered 1248 participants after applying inclusion and exclusion criteria.

Ethical Approval

This study was approved by the Ethical Committee No. H-2021-193 from REC at the University of Hail.

Collection of Samples and Data Management

The participants needed to determine their FBS level for seven days, and the average was considered for the record. So, the level of FBS mentioned against each participant is the mean

Table I. The drug classes available for T2DM and their respective mechanism.

Drug Class	Mechanism
Biguanides (Metformin)	↑ Glucose production by the liver ↑ Glucose Uptake by muscles
Sulfonylureas	↑ The pancreatic secretion of Insulin
GLP-1 receptor agonists	↑ Secretion of insulin for increased blood glucose ↓ Glucagon secretion by the pancreas stomach emptying is delayed ↑ Satiety
DPP-4 inhibitors	↑ Insulin secretion responding to higher blood glucose level ↓ Pancreatic glucagon release

value of FBS taken every morning for seven days. HbA1c was also considered for assessing the status of diabetes. HbA1c was done by the participants themselves from their nearest diagnostic centre. The questionnaire circulation and collection were done between October 2021 and April 2022. After collecting the questionnaires, the data was entered into Excel sheets. According to the answers of the participants, they were a group as follows:

- Participants taking only oral agents (single drug or multidrug) were grouped as Group 1.
- Participants taking oral agents and following diet modification actively were classified as Group 2.
- Participants taking oral agents, diet modification, regular exercise, and CAM were classified as Group 3.

Group 1 patients follow Single Approach Management for T2DM, while Group 2 and Group 3 patients follow Multi-Approach Management for T2DM. The questionnaire further recorded Oral Agents as Single drug or Combination therapy, Diet Modification as Mild-Moderate or Moderate-Severe, and Regular Exercise as Mild-Moderate and Moderate-Severe.

Inclusion Criteria

All the participants were clinically diagnosed patients with Type-2 Diabetes Mellitus. The survey was done only on the Saudi population, T2DM patients on active management. The participants needed to provide FBS levels for seven days and HbA1c.

Exclusion Criteria

The patients excluded from the study did not cooperate with the whole process and had an underlying condition with T2DM like hypertension. Some of the participants were also excluded based on the suspicion that the information provided to the participants may be false.

Diagnosis of Type-2 Diabetes Mellitus

The diagnostic criteria of Diabetes Mellitus Type-2 in this study were done by determining morning FBS and HbA1c. The diagnostic criteria of Diabetes Mellitus Type-2 in this study were done by determining morning FBS and HbA1c. The study considered FBS $\geq$ 126 mg/dL and HbA1c$\geq$6.5% as criteria. This criterion for determining HbA1c was supported by the Endocrine Society and World Health Organization (WHO) in 2009[26,27]. Studies confirmed that using FBS and HbA1c as the diagnostic criteria provides pre-analytical stability and greater correlation to microvascular complications[28,29]. National Health and Nutrition Examination Survey have suggested 6% to be the cut-off value of HbA1c while 6.2% was appropriated for the Indian population[30-32].

Statistical Analysis

The FBS and HbA1c were statistically correlated with the management strategy received by the participants and statistically determined which group of management strategies is the most significant and effective in lowering the FBS and HbA1c. The study conducted ANOVA for the statistical analysis between the measurements of FBS and HbA1c with the management strategies. This current study considered α=0.05 as the statistical significance of p-value.

Results

The study found that the age (mean±SD) of the patients in group 1 is 32.41±4.64 years old, patients in group 2 are 32.43±4.79 years old, and patients in group 3 are 32.63±4.56 years old. The study also found that there are 1248 participants enrolled in this survey. In group 1, there are 209 males (16.74%) and 203 females (16.26%). There are 206 males (16.5%) and 183 females (14.66%) in group 2 and group 3, there are 232 males (18.5%) and 215 females (17.22%). Figure 2 below shows the boxplot diagram of the study groups on their age characteristics. Table II shows the mean, median and standard deviation of the

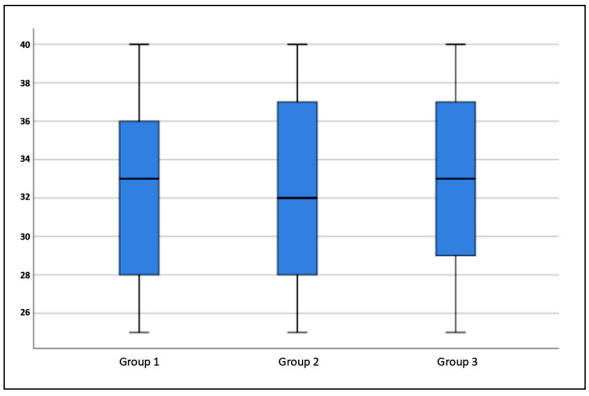

Figure 2. Box plot diagram of the age characteristics of the patients from each group.

Table II. FBS (mg/dL) and HbA1c (%) in each group.

		Mean	Median	SD
Fasting Blood Sugar (mg/dL)	Group 1	159.696	159	3.158
	Group 2	146.362	146	2.892
	Group 3	132.165	132	3.785
HbA1c (%)	Group 1	8.711	8.7	0.373
	Group 2	7.537	7.5	0.291
	Group 3	6.831	6.8	0.170

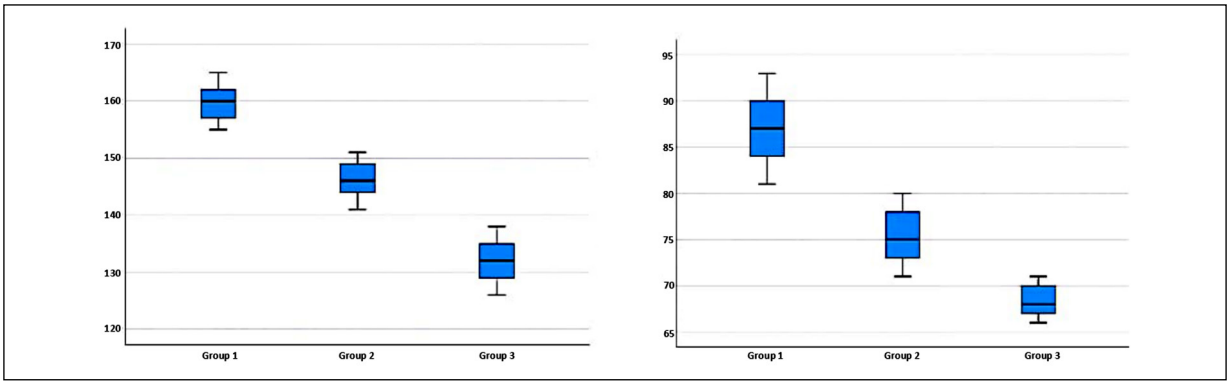

Figure 3. Box plot diagram showing FBS in each group of patients (*left*) and HbA1c in each group of patients (*right*).

patients in each group. The boxplot diagram depicts the distribution characteristics of FBS level findings in each group. Group 1 patients managed only on oral agents (either single or combination regimens) have the highest FBS. At the same time, Group 2 patients given diet modifications and oral agents showed significantly lower FBS than Group 1. The patients of Group 3, who were managed by Regular Exercise and Complementary and Alternative Medicines, in addition to Oral Agents and Diet Modifications, showed lower FBS findings than Group 1 and Group 2. Figure 3 reveals the boxplot diagram representing the FBS findings in each group.

The general characteristics of the FBS and HbA1c have been determined. Group 1 patients showed FBS level to be 159.69±3.15 mg/dL; Group 2 showed an FBS level of 146.36±2.89 mg/dL, and Group 3 had an FBS level of 132.16±3.78 mg/dL. Again, the level of HbA1c was found to be 8.71±0.37% in Group 1 patients, 7.53±0.29% in Group 2 patients and 6.83±0.17% in Group 3 patients.

The mean of FBS and HbA1c in each group is shown in the graph (Figure 4). The two charts have been depicted in the exact figure for efficient comparison. Figure 4 shows a steep downward trend of mean values of both FBS

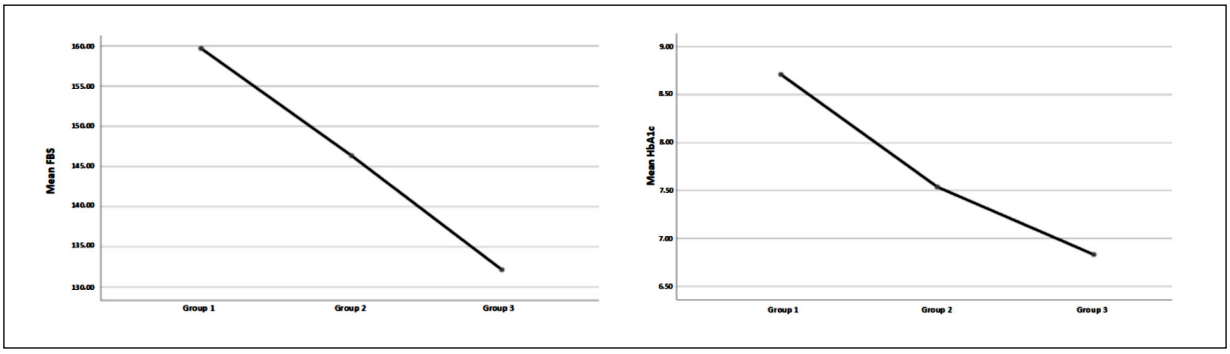

Figure 4. Mean of FBS (*left*) variation between groups and the same for HbA1c (*right*) has been depicted.

and HbA1c from Group 1 to Group 3. The findings of the other studies have also established similarities with our research. Hence, our results are almost similar to the previous studies. We have found a significantly improved level of FBS and HbA1c % in patients with regular exercise and diet regulation (used as an adjuvant to pharmacological treatment) compared to the patients who are only on pharmacological therapy alone.

The current study found 656 single oral agent users and 592 combination regimens users among all the study participants. The study also found that, among all participants, 511 patients were on mild to moderate diet modification while 325 patients were on moderate to severe diet modification. Two hundred eighty-two patients were on regular mild to moderate exercise, and 165 patients, who took part in this study, were on regular exercise at moderate to severe levels. Four hundred forty-seven patients also took CAM. These patients who were on diet modification; regular exercise and CAM are all in addition to oral agents. So, the current study finds that the addition of diet modification, regular exercise and CAM can significantly improve the level of HbA1c and FBS. The study also noted that 232 males and 215 females took CAM. Of 447 patients, 12 showed menstrual abnormalities (2.6%), and 18 had mild diarrhoea (4%). Table III presents the number of patients with their management strategies. Figure 5 shows the percentage of patients in each sub-category.

The study also found that there is a vital significance of lowering FBS and HbA1c with the management strategies ($p=0.000$). Group 1, group 2 and group 3 showed a significant decreasing trend in FBS level and HbA1c. Table IV shows the statistical analysis between the FBS and HbA1c in each group.

Group 1 patients were only on oral agents (monotherapy or combination therapy), and Group 2 patients were given diet modification along with oral agents. Group 3 patients were on regular exercise, CAM, diet modification and oral agents. The study found a strong association of improved HbA1c and FBS status with Group 3, lesser association with Group 2 and the least with Group 1.

Discussion

Our study has randomly selected participants based on inclusion and exclusion criteria to prevent any bias to affect our findings. A large sample is likely to increase the significance of the study findings concerning the population. The distribution of males and females are almost similar between the groups. The studies previously conducted pointed out improvement in the level of HbA1c and FBS in patients with diet modification and regular exercise as adjuvants[33-37], which is corresponding with our study findings. A similar finding has been observed in the case of HbA1c results in each group. Figure 5 shows the present mean value of the patients in each group. Table IV reveals the strong relationship with group 3 patients, concluding that HbA1c and FBS status improve when prescribed multi-approach management, including oral agents, diet modification, regular exercises, and adding complementary medicines. The improvement is statistically significant ($p=0.000$). There is a marked improvement in laboratory features of FBS and HbA1c, and hence, it must be included as guidelines for clinicians for managing T2DM. Many patients are still being managed only by oral agents. Studies show that most clinical management still involves only oral agents without lifestyle modification or exercise. Again, there are separate studies which have analytically shown that exercise and diet modifications have shown slight improvement, without using oral agents[35-38]. Therefore, our study is

Table III. Number of patients in each category as obtained from the questionnaire.

Category	Sub-category	Number of patients
Oral Agents	Single	656
	Combinations	592
Diet Modification	Mild-Moderate	511
	Moderate-Severe	325
Regular Exercise	Mild-Moderate	282
	Moderate-Severe	165
Complementary and Alternative Medicines		447

Table IV. Significance test between each parameter and management strategy.

Parameters	F (ANOVA)	Significance
Fasting Blood Glucose	7375.945	.000
HbA1c	4639.312	.000

done to evaluate the improvement in FBS and HbA1c by employing oral agents along with exercise and lifestyle modifications. In this study, Group 1 was revealed to have a much higher HbA1c and FBS level than Group 2 and Group 3, which shows that the improvement is significant in patients managed with exercise and diet management along with oral agents. There are other studies which also found that diet modification can result in alleviation of FBS and HbA1c levels[33,34]. Also, it is found that a strategically planned diet and consuming macronutrients in better proportion, lead to improvement in the general health of patients with T2DM. This contributes to the alleviation of blood sugar levels as well. A balanced diet and diet consisting of food items that can decrease the consumption of glucose may further contribute to the management of FBS and HbA1c in the long run by making glucose less available for digestive absorption[32,34]. It is also advisable that aerobic exercise should be carried out daily which can predominantly facilitate the breaking of muscle glycogen which, in turn, is derived from blood glucose and adipose fatty acids[31,33,34]. Another study pointed out that diet modification should be under strict guidelines. The guideline may include 50-60% of carbohydrates, about 15% of protein and cholesterol of less than 25%[35]. Other studies have found that maintaining nutrition according to practice guidelines has resulted in more than a 10% reduction in Fasting Blood Sugar and a significant decrease in HbA1c level after six months and three months of modified diet maintenance, respectively[36]. Table IV shows that the difference between FBS and HbA1c level have been managed with a strong significance between the groups (p=0.000). Cauza et al[37] have confirmed substantial improvement in blood glucose due to endurance training. The current survey-based research study has shown that adding diet modification over oral agents and adding exercise and CAM over oral agents and diet modification should improve the HbA1c and FBS status. Another study noted that resistance exercise could be considered responsible for significant improvement in fasting blood glucose levels[38].

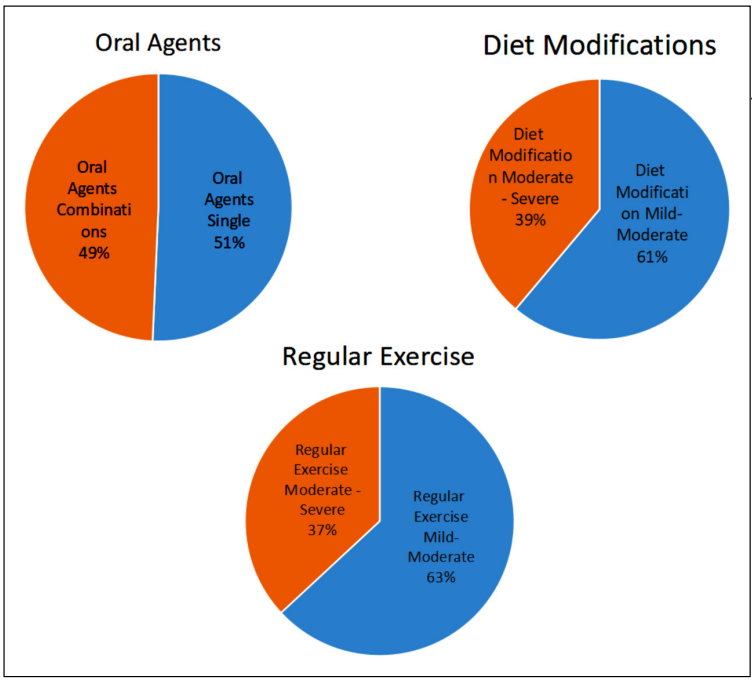

Figure 5. Percentage of patients in each subcategory as obtained from the questionnaire.

Conclusions

This current study has analytically proved that the addition of regular exercise, diet regulation and CAM will have greater control on the level of FBS and HbA1c. The reliability of this current study is considerable due to its large study sample. The significance is such that it should be included in the guideline. The clinicians should be encouraged to include non-pharmacological management to add to the overall treatment plan and pharmacological treatment. The study proves that diet modification and regular exercise contribute significantly to the management; they should be considered as necessary as oral agents. Therefore, prescribing only oral agents should be discouraged, while multi-approach management, including oral agents, diet modification, exercise, and CAM, should be incorporated into the management guidelines of T2DM.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

The study has obtained required consent from each participant and the whole study process has been conducted according to the principles of Declaration of Helsinki developed by World Medical Association.

Funding

This research has been funded by the Scientific Research Deanship at the University of Hail, Saudi Arabia, through project number RG 20165.

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