Evaluation of the therapeutic approach and outcome of type 2 diabetes mellitus management strategies in Cameroon.

ABSTRACT.

Introduction: Type 2 diabetes mellitus (T2DM) is a metabolic syndrome that is characterized by chronic hyperglycaemia, and can lead to chronic long-term complications. The prevalence of diabetes mellitus in Cameroon has been reported at 5.9 % in 2017. Studies conducted in 2011, showed that only 41 % of patients had a good glycaemic control which was, HbA1c < 6.5

The aim of this study was therefore to evaluate the treatment intensification with time in T2DM patients in the Yaoundé diabetic Centre in Cameroon.

Methods: The study was a cross-sectional analytical study. In a group of T2DM patients followed up at the National Obesity Centre (NOC) with poorly controlled blood sugar (HbA1c ≥ 7 %). The treatment intensification and outcome were evaluated between the periods January 2016 to April 2018. The data was collected from patients' medical booklet and through a face-to-face interviewer-administered questionnaire.

Results: One hundred and eleven patients (31 males, 27.9 % and 80 females, 72.1 %) were recruited. The mean age was between 59 ± 10 years and the mean duration of diabetes 8.6 ± 7.0 years. The patients' treatment consisted: 1) oral anti-diabetic (OAD) agents, monotherapy (24.3 %), bitherapy (28.8 %), tritherapy 2.7 %, 2) insulin only, 19.8 % and 3) insulin mixture, 24.3 %. The mean baseline HbA1c was 9.3 ± 2.0 %. Within the given follow-up time of 16 [11-21] months, only 40 out of the 111 patients had their treatment intensified and 71 had no intensification (therapeutic inertia) despite poor HbA1c levels. Among the 40 with intensification, 5 had immediate intensification and the proportions according to intensification delay ≤3 months, 3-6 months, 6-12 months and >12 months .

Conclusion: Therapeutic inertia affected two third of our population. Despite the high level of inertia, both patients with intensified treatment and non-intensified treatment reached treatment targets.

Keywords: Type 2 diabetes mellitus, glycated haemoglobin, treatment intensification, therapeutic inertia.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1-3]. There are mainly four types of DM: type 1 diabetes mellitus (T1DM) is immune-mediated and requires daily administration of insulin; type 2 diabetes mellitus (T2DM) is characterized by inadequate production of insulin and inability of the body to respond fully to insulin (insulin resistance). The gestational diabetes is glucose intolerance in hyperglycemia of variable severity with onset or first recognition during pregnancy [4], and complicates 2-4% of all pregnancies.. Weight gain and presence of placenta hormones increases insulin resistance [5].

Other specific types of diabetes include a wide variety of relatively unknown conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use [3-5]. The International Diabetes Federation (IDF) estimates that in 2017, 425 million people worldwide, representing 8.8 % of adults between 20-79 years had diabetes. The prevalence is predicted to increase to 629 million by 2045 if these trends continue. This is especially a concern in the Sub-Saharan Africa (SSA) which had a prevalence of 15.5 million people in 2017. Meanwhile, Cameroon registered a prevalence of 5.9 % in 2017 and caused about 15,757 diabetes related deaths that year [2, 6]. Thus, diabetes is an important public health problem.

The majority of DM is T2DM which accounts for 90-95 % of all the types. Associated to T2DM are long-term complications represented by cardiovascular diseases, cerebrovascular accidents, end-stage renal disease, retinopathy and neuropathies which are responsible for the major causes of morbidity, disability and premature death [1, 4]. Also, huge economic burdens are associated to diabetes affecting the families and nations [3, 7]. More so, Africa has the highest proportion of undiagnosed diabetes with over two-thirds (69.2 %) of people with diabetes unaware they have the disease [2].

The non-pharmacologic therapy (diet, exercise and weight loss) remains a critical component in the treatment of diabetes. However, pharmacologic therapy is often necessary to achieve optimal glycaemic control. Various classes of anti-diabetic agents target the different pathophysiologic factors contributing to diabetes: reduces insulin resistance [8] - Biguanides (Metformin),

Thiazolidinedione; stimulates insulin release [8, 9]. Sulfonylurea, Meglitinides; slows the digestive/absorptive process [10-11].- Alpha-Glucosidase Inhibitors; improves glucose-dependent insulin secretion [12]. Glucagon Like Peptide-1 (GLP-1) Agonists, Dipeptidyl Peptidase-4 (DPP-4) Inhibitors; blocks reabsorption of glucose in the kidneys [3, 12-14]. Sodium-Glucose Transporter-2 (SGLT-2) Inhibitors, enhances glucose-stimulated release of the GLP-1 [15]. Bile acid sequestrants (Colesevelam); increases insulin sensitivity - Dopamine-2 Agonists (Bromocriptine); slows gastric emptying - Amylin Analogues (Pramlintide) and facilitate glucose entry into the cell - Insulin [6, 16-18].

According to the IDF [2], healthy lifestyle is the first approach to T2DM management with an initiation of an oral medication when lifestyle modifications fail to achieve targets. The numerous anti-diabetic agents translates into more therapeutic options and complex decision-making [7]. These drugs can either be used alone or in combination. Metformin is the most commonly used initial treatment worldwide and subsequent treatment changes are based on failure to achieve target HbA1c after a three months period [8–10, 19]. With the failure of a maximal tolerated metformin dose to achieve HbA1c target over 3 months, treatment is intensified with a second orally administered agent (Sulfonylurea, DPP-4 inhibitors) or basal insulin. While initiation of insulin is not delayed in patients not achieving glycaemic goals [9, 20].

Despite the wide range of available medications and their benefits, studies have indicated that recommended glycaemic goals are achieved by less than 50 % of patients [21]. About 29 % of the patients have a good glycaemic control that is, HbA1C (<6.5 %) in Africa and only 41 % in Central Africa [23-24]. In Cameroon glycaemic control is poor with one in four known diabetic patients in a population-based survey having an optimal fasting blood glucose level [25]. As a result, hyperglycaemia and long-term complications are rising leading to increased morbidity and premature mortality, as well as increased costs to health services.

Several reasons may account for this poor glycaemic control and include poor adherence to treatment and lifestyle modifications [14, 26], poor blood glucose monitoring [15, 27], failure to keep appointments [5, 28] but more likely could reflect the contributions from the failure of clinicians to intensify therapy appropriately in individuals who are likely to benefit from such intensification - therapeutic inertia [17–19]. A recent study in the US revealed that the median time to treatment intensification among those in whom metformin monotherapy failed exceeded one year

while the median time to treatment intensification was 14 months overall [20, 29] although the ADA/EASD consensus recommendation is three months [5, 30].

Thus, from the facts from aforementioned studies, a majority of patients are not attaining the objectives set for the management of T2DM and a good prescription or therapeutic decision could lead to early optimal glycaemic control and thus reduce the risk of complications. This study sorts to evaluate treatment intensification over time in T2DM patients in Cameroon. With treatment intensification defined as an addition of an OAD or insulin to already existing drug (s) after an observation of a poor HbA1c level. To evaluate the notion of therapeutic inertia in type 2 diabetes patients and its impact on blood glucose targets.

MATERIALS AND METHODS

STUDY SITE

The study was carried out in the national obesity Centre (NOC) in the endocrinology and metabolic diseases service of the Yaoundé central hospital and happens to be a major teaching hospital in Yaoundé. NOC is a service specialized in endocrinology and a center for research projects aimed at sensitizing the public on diabetes and contributing to the development of national policies for the prevention, diagnosis and management of diabetes. It has a clinical research unit, a biochemistry laboratory, a unit for diet and nutrition and a unit for the free management of type 1 diabetes children

TYPE OF STUDY

This was a hospital-based cross-sectional analytic study carried out for a period of 7 months running from November 2017 to May 2018, with a period of recruitment of four months (January to April, 2018).

Study population

Target population: It consisted of patients diagnosed for type 2 diabetes already. They were patients recruited during external consultations, doing follow up at the NOC and through calls, for those patients who participated in a previous study at this center

Eligibility criteria

The inclusion included type 2 diabtes patients, an HbA1c $\geq$ 7 % between January 2016 and October 2017 with at least a follow-up time frame of six months from poor glycaemia. The patient must signed informed consent

Those not included in the study were patients with doubts about the type of diabetes, newly diagnosed diabtes patients, patients with a follow-up time in the clinic less than 6months and patients who were inconsistent at the clinic (less than two visits in the last 12 month)

SAMPLING

At the reception in the hospital, all the medical records of outpatients, as well as the register of H3A were screened to seek for eligible patients.

Therapeutic inertia.

This study evaluated therapeutic inertia and its impact on blood glucose targets through the consultation of patients' medical booklets at the hospital, but also the H3A register. The participants were screened amongst patients with T2DM who came for monthly consultations at the NOC while others were called using a database of a free HbA1c study done at this centre between March 2016 and March 2017 (H3A program). From this database, those with HbA1c ≥7% were called and invited. The study was explained to the patients with the use of an information sheet consent was obtained. A face-to-face interviewer questionnaire was used to collect data while information not given by the patient was completed from the medical booklet. Since there were no electronic records to obtain accurate medication histories of patients, only patient's medical booklets were used.

Patients who had not done a second HbA1c test, were educated on its usefulness and referred to a clinician for the test to be prescribed. The presence of this control HbA1c result called for a second appointment so that it could be noted. The questionnaire was available in the English and French language . In line with current views, therapeutic inertia was defined as the failure to intensify therapy (an addition in the number of drug classes) when indicated. It should be kept in mind that ADA guidelines state that HbA1c should be <7.0 %. By comparing the classes of anti-diabetic agents used at the start before the measured elevated HbA1c (index treatment) used for this study with those prescribed later or not, we established whether pharmacotherapy had been intensified; the researcher had to answer 'yes' or 'no' to questions about the action taken during each of the patients visit regarding anti-diabetic treatment after a poor baseline HbA1c ≥7 %: (1) anti-diabetic treatment has been maintained; (2) a new oral anti-diabetic treatment has been added (either metformin, sulphonylurea, glitazone, glinide, alpha-glucosidase inhibitor, dipeptidyl dipeptidase-4

inhibitor, or a combination of oral anti-diabetics); (3) insulin has been added; (4) the dose of some of the anti-diabetic agents has been increased; (5) drug classes have been switched.

Time to treatment intensification was calculated by subtracting the first date an elevated HbA1c was presented to the clinician from the first date of treatment intensification. From this calculation, they were grouped into immediate intensification (same day), delayed intensification and never intensified.

Judgment criteria

The time until treatment intensification had two subsets of patients:

- Proportion of patients that received treatment intensification which was either immediate or delayed, giving proportions that received intensification in less than or equal to 3 months, in 6 months, in 12 months and in greater than a year.

- Proportion of patients who never had their treatment intensified (till end of study) - (therapeutic inertia).

DATA ANALYSIS

All data collected were entered and statistical analysis performed using Epi info Version 3.5.4 software and results compiled with Microsoft Excel 2013. Chi II-test for categorical variables were used to compare groups (treatment intensified and therapeutic inertia) on various variables. The significant level was at 5 %, giving a statistical significance at p-value < 0.05. Kaplan-Meier analysis was performed for time until intensification to evaluate the probability for treatment to be intensified based on glycated haemoglobin levels (at <8 and ≥ 8 %), with the use of statistical package for social sciences (SPSS) version 20.0. Data were presented as mean and standard deviation (SD), frequency, percentage or ranges.

ETHICAL CONSIDERATIONS

Ethical clearance to carry out this study was obtained from the Institutional Research Ethics Committee of the Faculty of Medicine and Biomedical sciences of the University of Yaoundé I and the Center Regional Ethics Committee for Human Health Research The authorisation to carry out the study at the Yaoundé Central Hospital was obtained from the Director of the hospital The rights

of patients and workers in these hospitals were duly respected throughout this research in which participation was voluntary.

Nine hundred and fifteen patients' records were screened. One hundred and seventy two met up inclusion criteria. Sixty two were excluded; 28 patients had less than 2 visits for last 12 months and 15 patients had lost a section of their follow-up records, while 16 declined to participate. Thus, 111 patients participated. Figure 1 below shows the consort flow diagram of the study.

RESULTS

BASELINE CHARACTERISTICS OF THE POPULATION

Socio-demographic characteristics

Figure 1 shows the age and sex distribution for all participants. The population had 31 males (27.9 %) and 80 females (72.1 %). The ages ranged from 37 to 78years with a mean age of 59 ± 10 years.

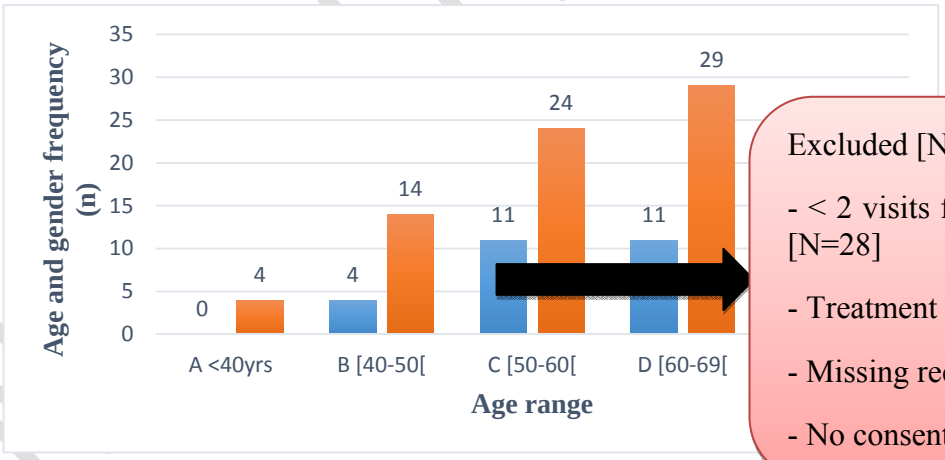

Figure 1: Age and Gender of the population

The majority of the population was from the West (43 %) and was married (52/111). The distribution for socio-demographic characteristic is presented on Table 1.

Table 1: Socio-demographic characteristics of the population

Characteristics	General population N (%) N=111
Region	

Centre	45 (40.5)
Far North	3 (2.7)
Littoral	5 (4.5)
North West	1 (0.9)
West	48 (43.2)
South	7 (6.3)
South West	2 (1.8)
Marital status	
Married	52 (47)
Single	12 (11)
Divorced	2 (2)
Widowed	41 (36)
Separated	1 (1)
F Co-habiting	3 (3)
Profession	
Civil servant	11 (9.9)
Private sector	13 (11.7)
Informal sector	20 (18.0)
Retired	23 (20.7)
Unemployed	44 (39.6)

Medical history

Diabetes duration

More than half of the participants had a diabetes duration of ≥ 5 years. Figure 2 demonstrates the ranges in duration of diabetes.

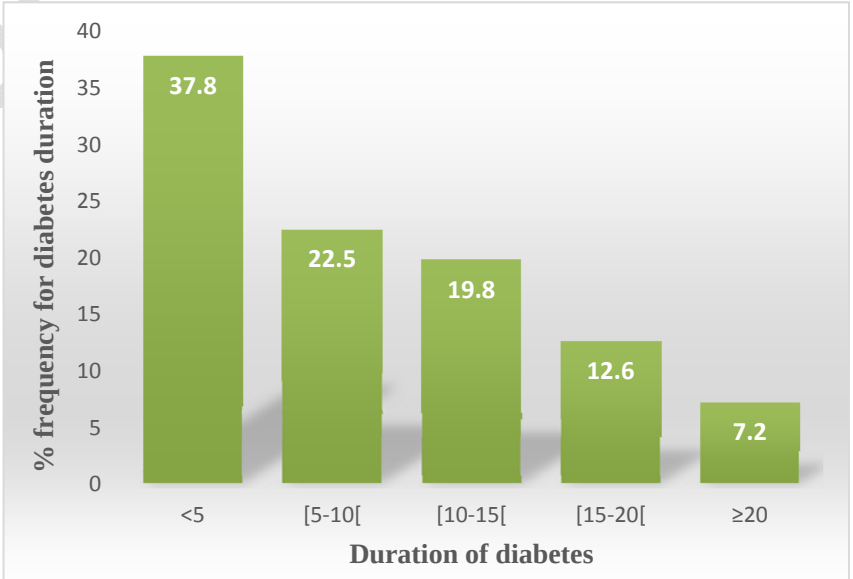

Figure 2: Diabetes duration range of study population

Treatment of the population

Twenty-six participants were on Metformin monotherapy, higher than other monotherapy and representing the second highest treatment category in the population. Most, 32 (28.8%) of the participants were on oral anti-diabetic (OAD) bitherapy, with Metformin and Sulfonylurea combination making up the greater therapy in the population. Insulin only was the therapeutic option for 22 participants. Table 2 gives the distribution by therapeutic option of study participants.

Table 2: Therapy of study participants

Treatment	Frequency (N)	Percentage (%)
OAD Monotherapy	**27**	**24.3**
Metformin	26	
Sulfonylurea (SU)	1	
OAD Bitherapy	**32**	**28.8**
Metformin/SU	29	
Metformin/DPP4i	3	
OAD Tritherapy	**3**	**2.7**
Meformin/SU/DPP4i	3	
Insulin only	**22**	**19.8**
Insulin/OAD mixture	**27**	**24.3**
Insulin/Metformin	19	
Insulin/SU	2	
Insulin/Metformin/SU	5	
Insulin/Metformin/DPP4i	1	
Total	111	100

Sixty-two percent of the participants were on more than 2 other non-diabetic medications in addition to their anti-diabetic medication. Figure 3 shows the distribution for the number of non-diabetic medication of the participants

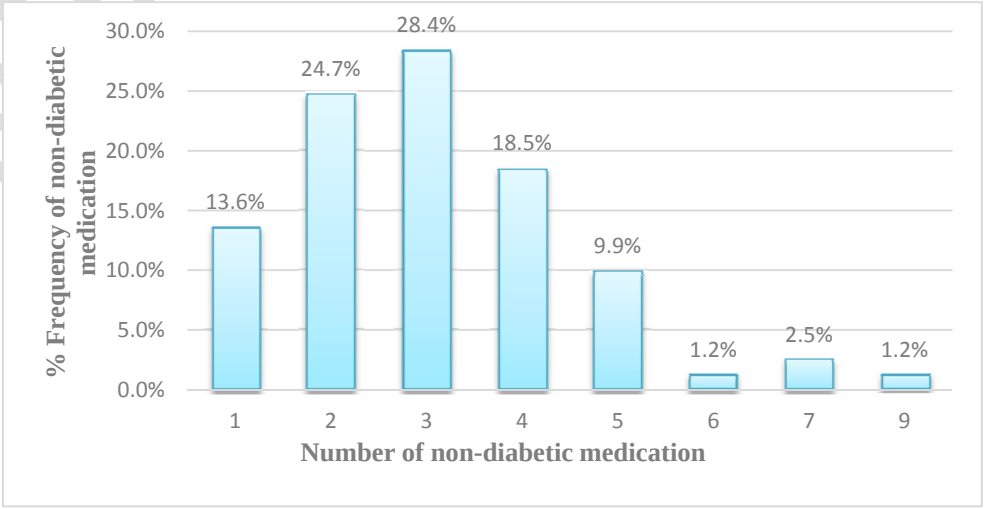

Figure 3: Number of non-diabetic medication of the study participants

Complications/Co-morbidities

Seventy-nine percent of the study population had at least a diabetic complication or a co-morbidity. Sixty percent were hypertensive and 26% had diabetic neuropathy. Table 3 below gives the dispersion for the other diseases present.

Table 3:Distribution for complications and co-morbidities in the population

Co-morbidity	Population N (%)
Diabetic retinopathy	16 (14)
Neuropathy	29 (26)
CVD	4 (4)
PVD	4 (4)
HT	67 (60)
Dyslipidemia	28 (25)

Glycaemic equilibrium

Patients on treatment are expected to reach targets of HbA1c < 7% faster. However, the population HbA1c ranged from 7 to 16% with a mean level of 9.3 ± 2.0%. Seventy-two percent of the population had a poor blood glucose control (HbA1c≥8%), with a mean capillary blood glucose of 200 ± 108 mg/dl. Figure 4 below gives the various percentages of participants according to cut-offs at <8%, <9%, <10% and ≥10%.

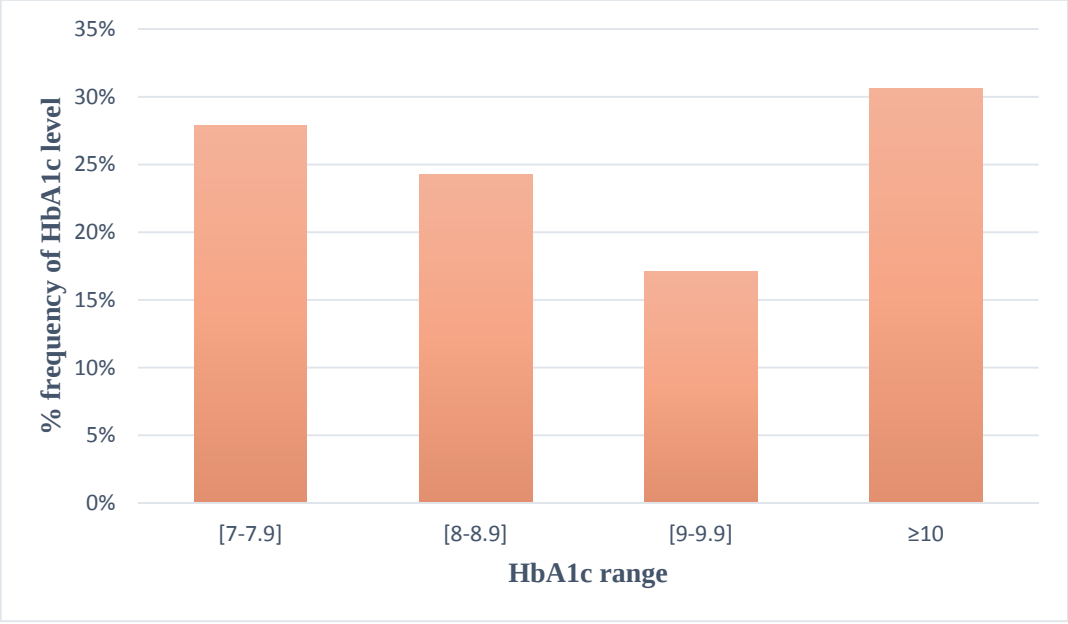

Figure 4: distribution of participants by HbA1c range

INTENSIFICATION OF TREATMENT IN PARTICIPANTS

The participants had a mean follow-up time of 16 [11-21] months from baseline with a mean of 4 ± 2 visits within past 12 months. Forty of them had their treatment intensified, 5 cases were immediate, but delayed in 35 patients [≤3 (20), 3-6 (7), 6-12 (3), >12 (5) months]. Seventy-one participants had no intensification. The mean HbA1c for the intensified group was 9.7 ± 2.0 % against therapeutic inertia group, 9.0 ± 1.9 %.

Among participants who had at least a medication added (40), 25 (62.5 %) had an addition of medication within 3 months from baseline result. No significant associations were seen to characterise this group. The distribution for the proportion of patients with time to treatment intensification is shown on figure 5 below.

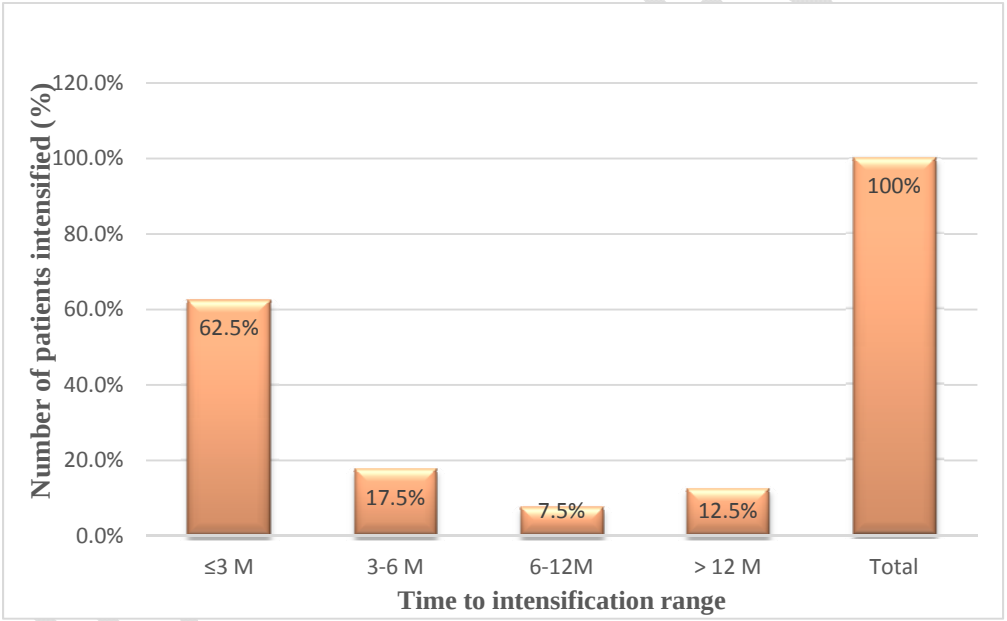

Figure 5: Proportion of patients intensified over time

Impact of intervention

The second HbA1c after the baseline was used to evaluate the evolution of blood sugar control in the 2 groups of participants. Twenty-nine of 40 of the intensified group had a second HbA1c test result and 54 for the non- intensified group. The HbA1c reduced in the global population, but more reduction was seen in the non -intensified group, 7.0 ± 1.6 % against 8.0 ± 2.0 %. Table 4 below shows the difference in HbA1c before and after intensification of treatment.

Table 4: Comparison of baseline and re-evaluated HbA1c (%)

Group of participants	Baseline	Control
All ***(N=111)***	9.3±2.0	7.4±1.7
Intensified ***(N=40)***	9.7±2.0	8.0±1.6
Non- intensified ***(N=71)***	9.0±1.9	7.0±1.6

FACTORS ASSOCIATED TO TREATMENT INTENSIFICATION

Several variables were analyzed for an influence on the decision to intensify patient's treatment. In a multivariable logistic regression model that accounted for age, gender, index treatment type (monotherapy, bitherapy, Insulin only, Metformin dosage ≥ 2000mg, Metformin/Sulfonylurea combination, Metformin/Insulin combination), duration of diabetes >5 years, number of other non-diabetic medications >2, the association to treatment intensification was stronger with patients age, index treatment (monotherapy, bitherapy, Metformin/Sulfonylurea combination, Metformin/insulin combination), duration of diabetes and number of other non-diabetic medications. Table 5 below gives the socio-demographic and medical history variables with the Odds ratios that influenced intensification. Older volunteers were less likely to have their treatment intensified with an Odds ratio (OR) of 0.10 95 % CI [0.01- 0.89], p-value <0.05. Participants with a duration of diabetes greater than 5 years were also less likely to receive intensification (p-value <0.05).

Table 5: Socio-demographic and medical history variables with the Odds ratios

Variable	OR (CI 95%)	P-value
Age (> 40 years)	0.10 [0.01- 0.89]	0.04
Duration of diabetes (>5years)	0.32 [0.13- 0.79]	0.01
Number of non-diabetic medications (>2)	0.37 [0.16- 0.85]	0.02

Those on monotherapy were 8 times more likely to receive intensification, than the other treatment types (p-value <0.05). Table 6 shows the distribution of baseline treatment and its influence on treatment intensification.

Table 6: Baseline treatment and association to treatment intensification.

Treatment type	OR (CI 95%)	P-value
Monotherapy	8.67 [2.49-30.28]	0.000
Bitherapy	0.20 [0.07-0.54]	0.002
Metformin/SU	0.14 [0.04-0.48]	0.002
Metformin/Insulin	0.09 [0.02-0.46]	0.000

Kaplan Meier distribution curve

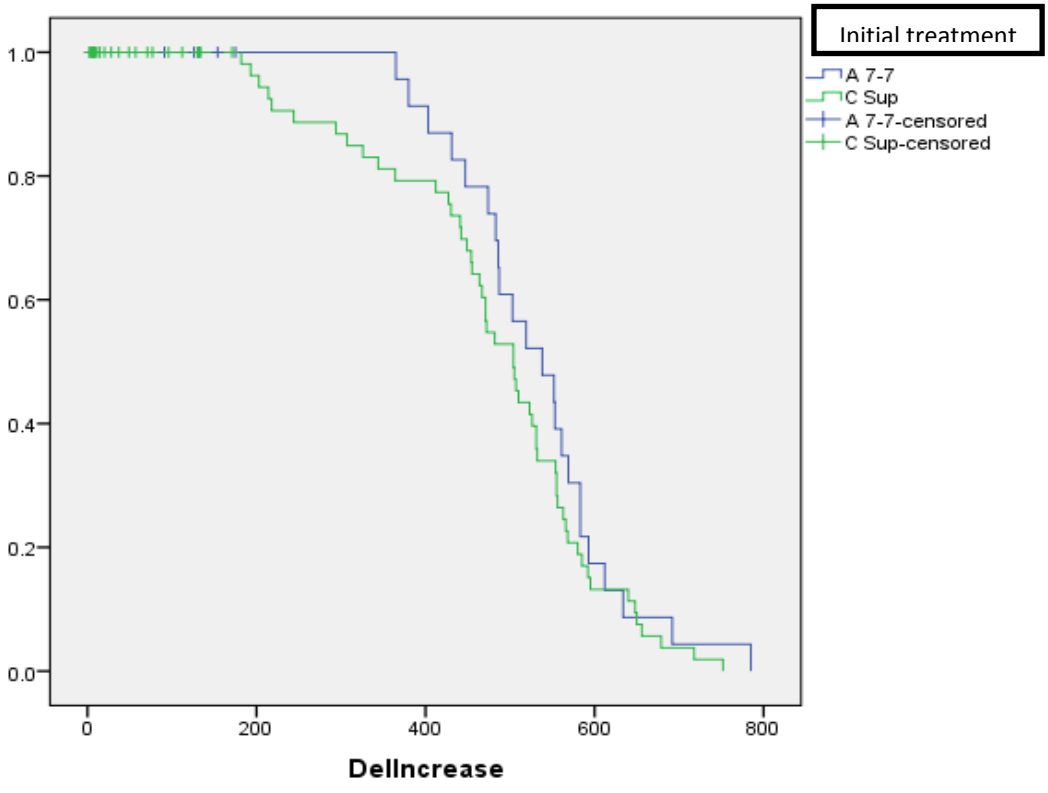

Figure 6: Kaplan-Meier curves for measuring time until intervention

Stratification by initial HbA1c 7–7.9 % and ≥ 8 %. The x-axis is presented in days, and the y-axis is presented as the cumulative probability of not experiencing an intervention. The influence of baseline HbA1c on inertia could not be seen clearly through analysis, so the Kaplan Meier curve was drawn to bring out this factor. The green line represents baseline hba1c ≥ 8 % and shows a lower probability for those in this group to stay without treatment intensified from about 180 days (6month) compared to those at HbA1c levels < 8 % (blue line) with a high probability to stay free from intensification.

DISCUSSION

This hospital-based cross-sectional analytical study was carried out with the main objective to evaluate the notion of therapeutic inertia in type 2 diabetes patients and its impact on blood glucose targets at the Yaoundé Central Hospital. The study consisted of a group of 111 T2DM volunteers, with a mean age of 59 ± 10 years, and diagnosed for diabetes since an average of 9 ± 7 years, with 2/3th of the participants on bitherapy and insulin therapy. For a period of about 16 months, treatment intensification was done only in 40 (36%) participants, and monotherapy was the only factor with strong positive association to treatment intensification. Forty-five percent of participants had HbA1c <7 % at re-evaluation.

An antidiabetic treatment was added in 36 % of the patients. Therefore, therapeutic inertia was present in 64 % of the patients. This result was comparable to the one reported by Sidorenkov et al.[23, 32]; for the same HbA1c goal with 1975 patients above target, not returning to control and not on maximum treatment, only 759 (38 %) received a treatment intensification (addition of 1 drug or dose). Yet, these results were high compared to other studies; by Paul et al [41] who had treatment intensified (addition of a second OAD or insulin to the first OAD) in 46 % of the patients and thus, a therapeutic inertia indication of 54 % at the same HbA1c goals [34-35]; while Tunceli et al. [36] had 4336 (56 %) with a treatment change, and 60 % representing an addition of a new class of antidiabetic agent, but recorded inertia in 35 % of patients.

Secondly, among those who received intensification, the proportion of patients with time to treatment intensification < 6 months was 80%, which is better than that reported by Paul et al [37,

41] with a proportion of 26 %. This study also had a median time to treatment intensification of 1 month, far less than all studies [median time of 14 months in the United State despite Metformin monotherapy failure [37, 38]; and median time of > 7.1, > 6.1 or 6.0 years, for patients taking one, two or three OADs respectively [39, 42].However, these results are not directly comparable, as the studies were differently designed.

Thirdly, 45% of the participants reached treatment targets, with both groups reaching targets. This is comparable to a study done in South Africa by Govender et al [12, 40]. However, the non-intensified group according to the results seemingly showed a better outcome (46 % above targets) than the intensified group (72 % above targets), that is, a mean HbA1c of 7.0 ± 1.6 % against HbA1c of 8.0 ± 1.6 %. Compared to a study mentioned above, 32 and 46 % of patients receiving early treatment intensification within 6 and 12 months of diagnosis continued to have poor glycaemic control over 2 years post diagnosis [HbA1c >7.5 %], while though 54 % of the patients never had treatment intensification their average HbA1c level remained above 6.5 %, but below 7 %, during 2 years post diagnosis. However, another study by Yu et al. [30, 41] demonstrated a better HbA1c outcome for early intensification (< 6 months) with mean HbA1c of 7.9 % against therapeutic inertia [late (≥6 months) or never intensified], with HbA1c of 8.2 %.

The observation of TI could have several reasons. First, the perception of intensification, which includes a dosage increase (of insulin or the same medication), and was shown to represent the greatest intervention according to the results. Among the total number of visits for the participants, a new drug was added in 40.2 % of cases (45 prescriptions), and doses increased in 59.8 % of cases (67 prescriptions) against 227 visits with Hba1c ≥7 %. Secondly, this could be influenced by adherence. Two-third of the population's treatment consisted of bitherapy, Insulin monotherapy (the therapeutic option for 19.8 % of the patients) and insulin mixture (24.3 %). Unlike other studies [43-45], the participants showed an early initiation of Insulin, probably due to specialty care [19, 46]. This tells the state and number of patients that could not attain glycaemic goals on Metformin alone. Patients on such treatment might be perceived as taking maximum treatment and patients' care focused on improving adherence (especially for those with poor observance).

Thirdly, it could be due inertia - proper, where clinicians overestimate the care provided; use "soft" reasons to avoid intensification of therapy; or due to lack of training, and lack of motivation to aim at achieving therapeutic goals earlier.

The outcome was observed to be better in the TI group probably due to aforementioned reasons, but also, perhaps better medication knowledge and improved self-monitoring by the patients. The re-evaluation of HbA1c was also observed at different time intervals from visit 1, it was not within the recommended time of 3 months, which could give a clearer picture for all patients at the same time-point with respect to intensification or not.

Lastly, this study demonstrated strong associations with monotherapy, age, duration of diabetes and other medications to treatment intensification. Older patients were less likely to have a treatment increase. Results regarding age from other studies seem conflicting. While Tunceli et al [36], Fu et al [37, 48]. all demonstrated a significant association between younger age and treatment increase, Mata-cases et al. demonstrated that age was the same for both the intensified and non-intensified groups. This perhaps because older patients often have more comorbidities and thus prone to polypharmacy, which could hinder treatment intensification. This factor may be verified by the significance in the association of the number of non-diabetic medication >2, to intensification (OR of 0.37, CI 95 % (0.16- 0.85), P-value= 0.018). This was comparable to the results of the study by Ajmera et al [6, 52] on the time to treatment intensification among elderly patients; with polypharmacy being the only significant barrier to treatment intensification in this group [49, 50]. In same like, a duration of diabetes greater than 5 years significantly hindered treatment intensification. This may be because patients with T2DM are often highly motivated near the time of diagnosis, so an early intensification could be done to improve glycaemic control soonest to prevent diabetes complications, but also not allow for time to pass and perhaps lose the patient to follow-up.

Participants on monotherapy were 8 times more likely to receive an intensification. Monotherapy is a treatment option in most newly diagnosed patients and ADA recommends a second-line therapy when a monotherapy management fails. Meanwhile, bitherapy was a significant barrier to treatment intensification, notably combinations of Metformin to a Sulfonylurea and Metformin to insulin [OR at 0.14, CI 95 % (0.04-0.48), p-value=0.0015 and OR at 0.09, CI 95 % (0.02-0.46), p-value=0.0034] respectively. According to the mechanisms of action of these two combinations (Metformin which improves peripheral glucose uptake and use; insulin stimulates glucose uptake

from the systemic circulation and suppresses hepatic gluconeogenesis, regulating glucose homeostasis, while Sulfonylureas stimulate insulin secretion by beta cells in the pancreas) and the pathophysiology of T2DM, the clinician may be prone to think such chronic regimen could give t patient maximum control [51].

At the end of this study, it was observed that it had the following limitations: the definition of TI was rigorous and a more rigorous level of HbA1c cut-off would be more appropriate and even if it were raised to chronic cut-off points such as >8 %, very few participants would be found. Lastly, the time during for the study was short to measure the impact of other interventions which could contribute to patient care and the influence of therapeutic inertia on the development of complications related to T2DM.

CONCLUSION

At the end of this study to investigate the therapeutic approach and outcome in type 2 diabetes mellitus management, the following conclusion was arrived at:

Therapeutic inertia affected two third of the population. Monotherapy was significantly associated to treatment intensification. A good proportion of patients with an indication of treatment intensification had it within three months from index elevated HbA1c. Both the intensified and non-intensified treatment groups had patients reaching treatment targets. Treatment intensification reduced the number of patients with poor glucose control.

Reference

1. World Health Organisation. Screening for Type 2 Diabetes. Report of a World Health Organization and International Diabetes Federation meeting. Geneva; 2003 p. 54. Report No.: 03.1.

2. International Diabetes Federation. International Diabetes Federation. IDF Diabetes Atlas [Internet]. 8th edn. Brussels, Belgium; 2017. 145 p. Available from: www.diabetesatlas.org

3. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B. Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care [Internet]. 2006 Aug 1 [cited 2017 Nov 28];29(8):1963–72. Available from: http://care.diabetesjournals.org/content/29/8/1963

4. Cheng AYY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. Can Med Assoc J [Internet]. 2005 Jan 18 [cited 2018 Apr 19];172(2):213–26. Available from: http://www.cmaj.ca/content/172/2/213

5. International Diabetes Federation. Global Guideline for Type 2 Diabetes. Clinical Guidelines Task Force [Internet]. Brussels, Belgium; 2012 [cited 2017 Nov 14]. 109 p. Available from: www.idf.org

6. American Diabetes Association. Standards of Medical Care in Diabetes 2017. CLINICAL AND APPLIED RESEARCH AND EDUCATION [Internet]. 2017 Jan;40. Available from: WWW.DIABETES.ORG/DIABETESCARE

7. Czupryniak L. Guidelines for the management of type 2 diabetes: is ADA and EASD consensus more clinically relevant than the IDF recommendations? Diabetes Res Clin Pract [Internet]. 2009 Dec 1 [cited 2017 Nov 25];86(Supplement 1):S22–5. Available from: http://www.sciencedirect.com/science/article/pii/S0168822709700051

8. Grant RW, Wexler DJ, Watson AJ, Lester WT, Cagliero E, Campbell EG, Nathan DM. How Doctors Choose Medications to Treat Type 2 Diabetes. Diabetes Care [Internet]. 2007 Jun [cited 2018 Jan 2];30(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3829641/

9. Sobngwi E, Ndour-Mbaye M, Boateng KA, Ramaiya KL, Njenga EW, Diop SN, Mbanya J-C, Ohwovoriole AE. Type 2 diabetes control and complications in specialised diabetes care centres of six sub-Saharan African countries: The Diabcare Africa study. Diabetes Res Clin Pract [Internet]. 2012 Jan 1 [cited 2017 Dec 7];95(1):30–6. Available from: http://www.sciencedirect.com/science/article/pii/S0168822711005602

10. Echouffo-Tcheugui JB, Kengne AP. Chronic non-communicable diseases in Cameroon - burden, determinants and current policies. Glob Health [Internet]. 2011 Nov 23 [cited 2017 Nov 28];7:44. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3251529/

11. Berhane Fseha. Glycemic Control and it's Associated Factors in Type 2 Diabetic Patients in Suhul Hospital, Northwest Tigray, Ethiopia. J Diabetes Metab. 2017;8(3).

12. Govender RD, Gathiram P, Panajatovic M. Poor control and management of type 2 diabetes mellitus at an under-resourced South African Hospital: is it a case of clinical inertia? South Afr Fam Pract [Internet]. 2017 Sep 18 [cited 2017 Dec 21];59(5):154–9. Available from: https://doi.org/10.1080/20786190.2017.1307909

13. Ziemer DC, Doyle JP, Barnes CS, Branch WT, Cook CB, El-Kebbi IM, Gallina DL, Kolm P, Rhee MK, Phillips LS. An Intervention to Overcome Clinical Inertia and Improve Diabetes Mellitus Control in a Primary Care Setting: Improving Primary Care of African Americans With Diabetes (IPCAAD) 8. Arch Intern Med [Internet]. 2006 Mar 13 [cited 2017 Dec 14];166(5):507–13. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/409945

14. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care. 2004 Jul;27(7):1535–40.

15. Kibirige D, Atuhe D, Sebunya R, Mwebaze R. Suboptimal glycaemic and blood pressure control and screening for diabetic complications in adult ambulatory diabetic patients in Uganda: a retrospective study from a developing country. J Diabetes Metab Disord [Internet]. 2014 Mar 4 [cited 2017 Dec 7];13:40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3974012/

16. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? Diabetes Care. 2005 Mar;28(3):600–6.

17. Fu AZ, Qiu Y, Davies MJ, Radican L, Engel SS. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. Diabetes Obes Metab. 2011 Aug;13(8):765–9.

18. World Health Organization. Tool for assessment of diabetes and diabetic retinopathy (TADDS). Geneva, Switzerland; 2015. 29 p.

19. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2010 Jan [cited 2017 Nov 28];33(Suppl 1):S62–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2797383/

20. American Diabetes Association. Classification and Diagnosis of Diabetes. Standards of Medical Care in Diabetes. 2015;38.

21. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047–53.

22. Mbanya J-C, Ramiaya K. Diabetes Mellitus. In: Jamison DT, Feachem RG, Makgoba MW, Bos ER, Baingana FK, Hofman KJ, Rogo KO, editors. Disease and Mortality in Sub-Saharan Africa [Internet]. 2nd ed. Washington (DC): World Bank; 2006 [cited 2017 Nov 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK2291/

23. Sidorenkov MM, Martin M. Zdanowicz. Essentials of pathophysiology for pharmacy. Washington, D.C: CRC Press pharmacy education series; 2011. 203–9 p.

24. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva, Switzerland; 2006 p. 50.

25. International Diabetes Federation. Type 2 Diabetes Clinical Practice Guidelines for Sub-Saharan Africa. Africa Region; 2006. 60 p.

26. Simpson SH, Lin M, Eurich DT. Medication Adherence Affects Risk of New Diabetes Complications: A Cohort Study. Annals of Pharmacotherapy [Internet]. 2016 Jun 17;1–16. Available from: aop.sagepub.com

27. Perreault S, Yu AYX, Côté R, Dragomir A. Adherence to antihypertensive agents after ischemic stroke and risk of cardiovascular outcomes. American Academy of Neurology. 2012 Nov;2037–48.

28. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab [Internet]. 2016 [cited 2017 Nov 28];20(4):546–51. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911847/

29. Lee PG, Halter JB. The Pathophysiology of Hyperglycemia in Older Adults: Clinical Considerations. Diabetes Care [Internet]. 2017 Apr 1 [cited 2018 Apr 19];40(4):444–52. Available from: http://care.diabetesjournals.org/content/40/4/444

30. Yu-Ju Tseng, Gregory Steinberg, Kathe P. Fox, Joanne Armstrong, Kenneth D. Mand. Antihyperglycemic Medications: A Claims-Based Estimate of First-line Therapy Use Prior to Initialization of Second-line Medications. Diabetes Care. 2017 Nov;40:1500–1505.

31. Susan Cornell. The AADE 2017 Pharmacotherapy Bootcamp. Lecture presented at: Midwestern University; 2017; Chicago College of Pharmacy.

32. Arun Chaudhury, Chitharanjan Duvoor, Vijaya Sena Reddy Dendi, Shashank Kraleti, Aditya Chada, Rahul Ravilla, Nawal Singh Shekhawat, Maria Theresa Montales, Kevin Kuriakose, Appalanaidu Sasapu, Alexandria Beebe, Naveen Patil, Chaitanya K. Musham, Govinda Prasad Lohani, Wasique Mirza. Clinical Review of Antidiabetic Drugs: implications for Type 2 Diabetes Mellitus Management. Front Endocrinol [Internet]. 2017 Jan;8(6). Available from: www.frontiersin.org

33. Michelle A. Clark, Richard Finkel, Jose A. Rey, Karen Whalen. Lippincott's Illustrated Reviews: Pharmacology. 5th edition. 2012.

34. DPP-4_inhibitors [TUSOM | Pharmwiki] [Internet]. [cited 2018 May 28]. Available from: http://tmedweb.tulane.edu/pharmwiki/doku.php/dpp-4_inhibitors

35. Hansen M, Sonne DP, Mikkelsen KH, Gluud LL, Vilsbøll T, Knop FK. Effect of bile acid sequestrants on glycaemic control: protocol for a systematic review with meta-analysis of randomised controlled trials. BMJ Open [Internet]. 2012 Jan 1 [cited 2018 Apr 19];2(6):e001803. Available from: http://bmjopen.bmj.com/content/2/6/e001803

36. Tunceli IP, Malhotra A, Kudyar S, Gupta AK, Kudyar RP, Malhotra P. Sodium glucose co-transporter inhibitors – A new class of old drugs. Int J Appl Basic Med Res [Internet]. 2015 [cited 2018 Apr 19];5(3):161–3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606572/

37. Fu OL, DeFronzo RA. Bromocriptine: A Sympatholytic, D2-Dopamine Agonist for the Treatment of Type 2 Diabetes. Diabetes Care [Internet]. 2011 Apr 1 [cited 2018 Apr 19];34(4):789–94. Available from: http://care.diabetesjournals.org/content/34/4/789

38. Arthur C. Guyton, John E. Hall. Textbook of Medical Physiology. ELEVENTH EDITION. Philadelphia, Pennsylvania: Elsevier Suanders; 2006. 961–963 p.

39. Donner T. Insulin – Pharmacology, Therapeutic Regimens And Principles Of Intensive Insulin Therapy. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2018 Apr 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK278938/

40. Madhu S, Srivastava S. Diabetes Mellitus: Diagnosis and Management Guidelines. JIMSA. 2015 Mar;28(1):47–50.

41. Paul GH, Essien O, Otu A, Umoh V, Enang O, Hicks JP, Walley J. Intensive Patient Education Improves Glycaemic Control in Diabetes Compared to Conventional Education: A Randomised Controlled Trial in a Nigerian Tertiary Care Hospital. PLoS ONE [Internet]. 2015 Jan 3 [cited 2017 Nov 3];12(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5207750/

42. Khunti K, Gomes MB, Pocock S, Shestakova MV, Pintat S, Fenici P, Hammar N, Medina J. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: A systematic review. Diabetes Obes Metab [Internet]. [cited 2017 Dec 6];n/a-n/a. Available from: http://onlinelibrary.wiley.com/doi/10.1111/dom.13088/abstract

43. Mata-Cases M, Benito-Badorrey B, Roura P, Franch-Nadal J, Pepió J, Saez M, Tuero G. Clinical inertia in the treatment of hyperglycemia in type 2 diabetes patients in primary care. Curr Med Res Opin. 2013 Aug 14;29.

44. Reach G, Pechtner V, Gentilella R, Corcos A, Ceriello A. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab [Internet]. 2017 Dec 1 [cited 2017 Dec 7];43(6):501–11. Available from: http://www.sciencedirect.com/science/article/pii/S1262363617304676

45. O'Connor PJ, Sperl-Hillen JAM, Johnson PE, William A. Rush, George Biltz. Clinical Inertia and Outpatient Medical Errors. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Rockville (MD). Agency Healthc Res Qual US [Internet]. 2005 Feb;2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20513/?report=reader#!po=15.5172

46. Pantalone KM, Wells BJ, Chagin KM, Ejzykowicz F, Yu C, Milinovich A, Bauman JM, Kattan MW, Rajpathak S, Zimmerman RS. Intensification of Diabetes Therapy and Time Until A1C Goal Attainment Among Patients With Newly Diagnosed Type 2 Diabetes Who Fail Metformin Monotherapy Within a Large Integrated Health System. Diabetes Care [Internet]. 2016 Sep 1 [cited 2017 Dec 14];39(9):1527–34. Available from: http://care.diabetesjournals.org/content/39/9/1527