Study of Prescription Pattern and Factors Associated with Clinical Outcomes in Type 2 Diabetes Mellitus with Reference to Short Term Glycemic Control

Shakya Shrestha S,[1,2] Palanchoke S,[1] Shrestha R,[1,2] Bhatta RD[3]

[1]Department of Pharmacology,

[2]Pharmacovigilance Unit,
Research and Development Division,

[3]Department of Clinical Biochemistry,

Kathmandu University School of Medical Sciences

Dhulikhel, Kavre, Nepal.

Corresponding Author

Sony Shakya Shrestha

Department of Pharmacology,

Kathmandu University School of Medical Sciences,

Dhulikhel, Kavre, Nepal.

E-mail: sonyshakya@hotmail.com

ABSTRACT

Background

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Though oral hypoglycemic agents (OHAs) or/and insulin are prescribed to control the hyperglycemia, still glycemic control is not seen in most of the cases. Evaluating the treatment pattern including the glycemic control and associated factors are of utmost importance for better patient care.

Objective

To investigate the treatment pattern and short term glycemic control among Type 2 Diabetes Mellitus (DM2) patients and study the factors associated with it.

Method

Patients meeting the inclusion criteria with DM2 attending laboratory or Out-Patient Department or Emergency Department in Dhulikhel Hospital and patients who were admitted to the ward taking various OHAs and/or insulin at the time of data collection were considered. Informed consent was taken prior to the interview. The collected data was entered as well as analyzed using the SPSS (Statistical Package for Social Sciences) version 21.0 and the p-value <0.05 was considered statistically significant.

Result

Among the 118 patients, 50.8% of them were males. Majority (28%) of the patients belonged to the age group of 51-60 years. Out of the 118 patients, 22% had their fasting blood glucose (FBG) level under control whereas 78% had uncontrolled FBG level. Metformin was the most (28%) commonly prescribed drug. Significant association was found between gender; knowledge about disease and medication with short term glycemic control (p=0.034, p=0.004 ans p=0.039 respectively).

Conclusion

All the patients enrolled in this study were under various anti-diabetic medications, however, majority of them didn't have their glycemia under control. Significant association was found between FBG level and gender, knowledge about disease and knowledge about medication.

KEY WORDS

Diabetes, Glycemic control, Insulin, Oral hypoglycemic agents

INTRODUCTION

Type 2 Diabetes Mellitus (DM2) is recognized as one of the major global epidemic, with an increasing prevalence in many developed and/or developing Asian countries.[1,2] According to the International Diabetes Federation (IDF), relative to neighboring countries such as Pakistan, Sri Lanka, and Bangladesh, Nepal has a higher prevalence of DM2 and impaired glucose tolerance.[3] More than 77 % of morbidity and 88 % of mortality due to DM occur in low and middle-income countries.[4] In young adults, the absolute incidence of DM2 is low, but a marked surge in diabetes-associated morbidity has been reported.[5] These symptoms and complications can be prevented or treated by various non-pharmacological and pharmacological approaches.

Oral hypoglycemic agents (OHAs) are the major treatment for DM2 patients and these agents are targeted for intensive blood-glucose control which leads to a decrease in microvascular complications, such as nephropathy and retinopathy.[6] It is also suggested to be advantageous to introduce insulin therapy much earlier in the disease course to achieve tight glycemic control.[7] Treatment with these various agents is known to improve glycemia, despite of this also glycemic control in DM2 patients is very challenging indicating role of other factors as well. However, how often various agents prescribed for DM2 can attain controlled blood glucose level and evaluation of various factors associated with it has not been documented in Nepal till date. Therefore, our study attempted to address the pattern of use of anti-diabetic drugs along with the glycemic control provided by them and elucidate factors associated with it.

METHODS

A cross sectional study was conducted in Dhulikhel Hospital, Kathmandu University Hospital, Dhulikhel. An ethical approval was taken from Institutional Review Committee, Kathmandu University School of Medical Sciences (IRC/KUSMS). All patients diagnosed of DM2 using at least one anti-diabetic drug, either insulin or OHAs or their combination for at least a month satisfying inclusion criteria were included in the study. The inclusion criteria were; a) all the DM2 patients who were willing to give informed consent and visited laboratory or Out-Patient Department or In-patient department or Emergency Department in Dhulikhel Hospital, b) Patients who had discontinued medication at some point of time but has restarted medication for at least one month.

Patients who met the inclusion criteria were informed about the study being done and about their contribution in this study. After taking informed consent from the patients, they were directly interviewed using semi-structured questionnaire. The information regarding age, gender, education, occupation etc were recorded. Further information related to the use of insulin and/ or OHAs

and factors associated with glycemic control like name of the drugs, duration of use, number of drugs, patients' perception of drug and disease, their knowledge etc were recorded and filled in the semi-structured questionnaire. Information regarding laboratory investigations: fasting blood glucose (FBG) test and post-prandial blood glucose test where feasible were obtained from patients' OPD card.

Collected data was entered into Statistical Package for Social Sciences (SPSS) Version 21.0. The detail of working procedure is shown in figure 1. The quantitative data was expressed in percentages and mean ± standard deviation (SD). Similarly, the qualitative data was analyzed using Pearson's Chi Square test and Shapiro-Wilk test. The p-value <0.05 was considered statistically significant.
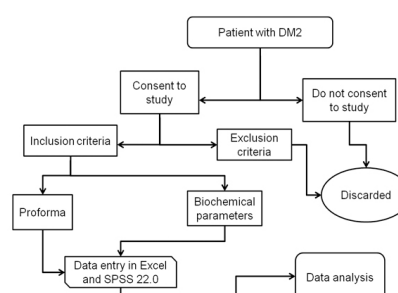

**Figure 1.** Flow chart showing stepwise procedure of data collection and analysis

RESULTS

Among the 118 patients included in the study, 49.2% (n=58, 49.2%) of them were females and 50.8% (n=60, 50.8%) were males. Majority (28% (n=33, 28%)) of the patients were between 51-60 years and their mean (±SD) age was 57.07 years (±13.07). Regarding literacy of patients, 43.2% (n=51, 43.2%) were literate and 56.8% (n=67, 56.8%) were illiterate. Among 118 patients, the mean (±SD) value of FBG was 145.23 mg/dl (±65.69). The mean (±SD) of PPBG among 95 patients was 233.68 mg/dl (±123.42).

Among 118 patients, most of the patients (44.92% (n=53, 44.92%)) were prescribed with two different drugs and majority (22.9% (n=27, 22.9%)) of the patients were prescribed with biguanides and sulphonylureas (SUs) followed by 18.6% (n=22, 18.6%) patients prescribed with biguanides and insulin. The most commonly prescribed drug as monotherapy was biguanides (28% (n=33, 28%)). The details of the pattern of use of hypoglycemic agentsanti-diabetic drugs are shown in figure 2.
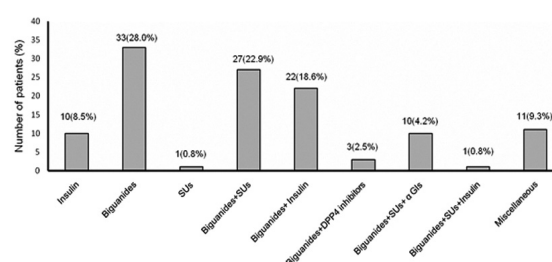
Figure 2. The details of the pattern of use of anti-diabetic drugs.

Regarding the duration of medication, majority (38.1% (n=45, 38.1%)) of the patients were under medication for 1-12 months followed by 31.4% (n=37, 31.4%) of patients for more than 60 months as shown in figure 3.
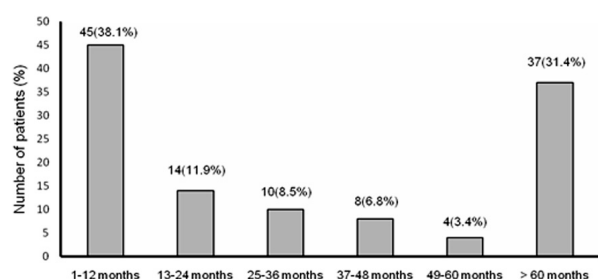
Figure 3. Bar diagram showing duration of use of anti-diabetic drugs among 118 patients.

Comparing glycemic control of 118 patients prescribed with various anti-diabetic drugs, majority of the patients have uncontrolled FBG and PPBG level irrespective of the number of drugs and duration of medications as shown in Table 1.

There was no significant association of glycemic control with age, literacy, diet restriction, regular exercise, regular visit to physician, social support and medication affordability. A significant association was found between gender and short term glycemic control (FBG level) (p=0.034); knowledge about disease and FBG level (p =0.004) and knowledge about medication and FBG level (p = 0.039) as shown in Table 2.

Table 1. Anti-diabetic drugs with regards to short term glycemic control (FBG and PPBG level)

Variables	Total (N)	Controlled FBG[†] (n=26) No (%)	Uncontrolled FBG[‡] (n=92) No.(%)	p-value	Total (N)	Controlled PPBG[*] (n=14) No.(%)	Uncontrolled PPBG[$] (n=81) No.(%)	p-value
Drugs								
Biguanides	33	8 (24.24)	25 (75.76)	0.692	22	6 (27.27)	16 (72.72)	0.295
Sulphonylureas	1	1(100)	0(0)		1	0 (0)	1 (100)	
Insulin	10	1(10)	9 (90)		6	1(16.66)	5 (83.34)	
Biguanides+ Sulphonylureas+α glucosidase inhibitors	10	2 (20)	8(80)		5	0(0)	5 (100)	
Biguanides+DPP4 inhibitors	3	0(0)	3 (100)		2	0(0)	2 (100)	
Biguanides+Sulphonylureas	27	7(25.92)	20 (74.07)		27	5 (18.51)	22 (81.48)	
Biguanides+Insulin	22	5 (22.72)	17 (77.27)		19	2 (10.52)	17 (89.48)	
Biguanides+Sulphonylureas+Insulin	1	0 (0)	1 (100)		4	0 (0)	4 (100)	
Miscellaneous	11	2(18.18)	9 (81.81)		9	0(0)	9 (100)	
No. of drugs								
Single drug	44	10 (22.72)	34 (77.27)	0.895	44	7 (24.13)	22 (75.87)	0.053
Two drugs	57	13 (22.81)	44 (77.19)		57	7 (13.46)	45 (86.54)	
> 2 drugs	17	3 (17.64)	14 (82.36)		17	0(0)	14 (100)	
Duration of medication								
1-12 months	45	12 (26.66)	33 (73.33)	0.107	45	7 (17.95)	32 (82.05)	0.895
13-24 months	14	0 (0)	14 (100)		14	1 (9.09)	10 (90.90)	
25-36 months	10	3 (30)	7 (70)		10	0 (0)	9 (100)	
37-48 months	8	3 (37.50)	5 (62.50)		8	4 (66.66)	2 (33.33)	
49-60 months	4	1 (25)	3 (75)		4	0(0)	3 (100)	
> 60 months	37	7 (18.90)	30 (81.08)		37	2 (7.4)	25 (92.60)	

[†]Patients whose FBG level complies with the treatment goal by American Diabetes Association (ADA): ≤ 130 mg/dl
[‡]Patients whose FBG level is > 130 mg/dl
[*]Patients whose PPBG level complies with the treatment goal by American Diabetes Association (ADA): ≤ 180 mg/dl
[$]Patients whose PPBG level is > 180 mg/dl

DISCUSSION

Glycemic control is one of the main goals for treating diabetic patients to produce near-normal glucose levels to prevent the development of diabetic complications.[8] Therefore, it is important to understand how often various drug therapies can attain the glycemic target level and various factors associated with it.

In this study, almost equal numbers of male and female patients were enrolled. The result was consistent with previous study done by National Health and Nutrition Examination Survey group in which the overall prevalence was similar for both gender.[9] However, several other studies have shown different prevalence among the male

Table 2. Demographic and other charecteristics of 118 patients with regards to short term glycemic control (FBG and PPBG levels)

Variables	Total (N)	Controlled FBG[†] (n=26) No(%)	Uncontrolled FBG[‡] (n=92) No.(%)	p-value	Total (N)	Controlled PPBG[*] (n=14) No (%)	Uncontrolled PPBG[$] (n=81) No.(%)	p-value
Age (years)								
< 30	1	0(0)	1(100)	0.938	1	0(0)	1(100)	0.295
31-40	14	3(21.43)	11(78.57)		13	3(23.07)	10(76.93)	
41-50	25	5(20)	20(50)		22	3(13.63)	19(86.36)	
51-60	33	9(27.27)	24(72.73)		27	3(11.11)	24(88.88)	
61-70	28	6(21.43)	22(78.57)		21	4(19.04)	17(80.95)	
> 70	17	3(17.65)	14(82.35)		11	1(9.09)	10(90.90)	
Gender								
Male	60	18(30)	42(70)	0.034	48	7(14.58)	41(85.42)	0.966
Female	58	8(13.79)	50(80.59)		47	7(14.89)	40(85.10)	
Literacy								
Literate	51	13(25.49)	38(74.51)	0.429	46	7(15.21)	39(84.78)	0.898
Illiterate	67	13(19.41)	54(80.59)		49	7(14.28)	42(85.71)	
Diet restriction								
Yes	101	22(21.78)	79(78.22)	0.873	82	12(1.46)	70(98.54)	0.944
No	17	4(23.53)	13(76.47)		13	2(15.38)	11(84.62)	
Regular Exercise								
Yes	69	14(20.29)	55(79.71)		62	10(16.12)	52(83.88)	0.595
No	49	12(24.49)	37(75.51)		33	4(12.12)	29(87.88)	
Regular visit to physician								
Yes	104	25(24.03)	79(75.96)	0.261	86	14(16.27)	72(83.88)	0.082
No	13	1(7.69)	12(92.31)		9	0(0)	9(100)	
Knowledge about disease								
Yes	18	9(50)	9(50)	0.004	15	4(26.66)	11(73.34)	0.184
No	100	17(17)	83(73)		80	10(12.5)	70(84.95)	
Knowledge about medication								
Yes	100	25(25)	75(75)	0.039	79	13(16.45)	66(83.54)	0.252
No	18	1(5.55)	17(94.45)		16	1(6.25)	15(93.75)	
Social support								
Yes	17	3(17.65)	14(82.35)	0.63	9	1(11.11)	8(88.89)	0.739
No	101	23(22.77)	78(77.23)		86	13(15.11)	73(84.89)	
Medication affordability								
Yes	75	20(26.67)	55(73.33)	0.109	61	11(18.03)	50(81.97)	0.225
No	43	6(13.95)	37(86.05)		34	3(8.82)	31(91.18)	

[†]Patients whose FBG level complies with the treatment goal by American Diabetes Association (ADA): ≤ 130 mg/dl
[‡]Patients whose FBG level is > 130 mg/dl
[*]Patients whose PPBG level complies with the treatment goal by American Diabetes Association (ADA): ≤ 180 mg/dl
[$]Patients whose PPBG level is > 180 mg/dl

and female.[10-12] In a study done by Karki et al, most of the patients were males.[13] Similarly, another study done by Shrestha et al. found that DM2 was more common in females than in males.[14] The variation in prevalence pattern among both gender might be due to the reason of disparity in between males and females in health seeking behavior and access to care.[15]

Our study showed that majority of the DM2 patients were between the age group of 51-60 years followed by individuals belonging to 61-70 years old. The result was consistent with another study in which the prevalence of DM2 was high in age group of 41-60 years.[14,16] Similarly, a study done by UKPDS Group has also shown that the mean age group of DM2 patients was 53 years.[17] It might

be because patients of this age group are more prone to stressful life and poor eating habits because of their busy schedule. In addition to this, several studies have shown that DM2 and its complications are strongly associated with emotional and psychological stress which might be associated with the majority of the patients belonging to the age group of 51-60 years in this study.[18,19]

Most of the patients in this study were treated with biguanides (metformin). This result was consistent with another study done by Holman, which reported the decreasing use of monotherapy with sulfonylureas and an increasing use of biguanides.[20] A similar prescribing trend was also reported in another study.[21] Several studies had observed that metformin alone and metformin combination were the commonly prescribed antidiabetic drugs.[22-24] Likewise another study has shown that metformin was more efficacious than the DPP-4 inhibitors, thiazolidinediones or sulphonylureas in lowering blood glucose level.[25] Metformin is being considered as the first line agent in DM2 patients including obese ones because of its effectiveness in lowering blood sugar and that it preserves beta-cell functions.[26,27] It is also associated with fewer adverse effects compared with other anti-diabetic drugs.[17] According to Bailey, metformin also does not exacerbate hyperinsulinemia, appears to combat the fundamental problem of insulin resistance, benefits associated dyslipidemia and may offer other potentially vasoprotective effects.[27] It has also been observed that the beneficial effects of metformin are related to its potent insulin-sensitizing effects.[28,29] Studies have shown that metformin offers protection from cardiovascular disease.[29,30] In the UKPDS, metformin had decreased the risk of mortality and morbidity in obese patients with DM2 who had cardiac disease.[17] A study has also shown that taking metformin may also be associated with reduced risk of cancer in patients with DM2.[31]

In this study a considerable number of patients were also prescribed with insulin, SUs and various other combinations. This type of treatment pattern has been seen in other studies in which the patients were prescribed with sulphonylureas and insulin.[32,33] In a study, it showed that insulin was better than other anti-hyperglycemic agents in reducing FBG concentrations.[32] The reason for this may be because oral agents reduce post-prandial as well as FBG level, whereas basal insulin supply only reduced basal glucose concentrations.[32] The reason for prescribing insulin along with other diabetes medication may also be associated with less Alzheimer neuropathology.[34] In previous study it has been shown that it may be advantageous to introduce insulin therapy much earlier in the disease course to achieve tight glycemic control in DM2 patients.[35] Our study showed that insulin is not prescribed as much as metformin. There is evidence which suggests that more than one-quarter of patients refuse insulin therapy once it is prescribed.[36] The reason for this negative attitude towards insulin was the belief that beginning insulin therapy would indicate that they had failed proper diabetes self-management.[36] Some patients may associate insulin therapy with a sense of personal failure due to common physician practice and there is a possibility that insulin therapy may be used as a threat to motivate better patient cooperation.[37]

In a study done by Kilbourne et al. it showed that majority of the patients had a prescription for glyburide rather than metformin.[38] In our study also such type of prescription pattern was recorded, although it was less. Similar result was shown in previous studies, in which the patients received sulphonylureas after discontinuing insulin.[39,40]

Along with metformin, insulin and sulphonylureas, various other drugs were also prescribed along with it. These include various newer agents like DPP-4 inhibitors, thiazolidinediones, along with many others. According to another study, several recently released medications have shown rapid adoption into practice.[41] Many of these newer therapies are said to have made therapy more convenient and may have potentially lowered the risk of treatment-associated complications.[41] These new compounds, although costlier than their older counterparts, are promoted as they are more convenient and have enhanced ability to achieve glycemic control.[42]

In this study, in majority of the patients under one or more anti-diabetic agents there was poor short term glycemic control. It was also seen that most of the patients were under polytherapy rather than monotherapy. This finding was consistent with a study conducted by Birkeland et al. in which there was rapid deterioration of glycemic control in the patients under anti-diabetic drugs (SU or insulin).[43] Such poor glycemic control with anti-diabetic agents might have been because of the nature of disease itself which is not a stable condition and deteriorates consistently in nearly all patients even if they are under medications as suggested by Birkeland, et al.[43] The result was consistent with a study done by Baviera, et al., which showed that there was a rise in the number of those receiving two different oral anti-diabetic agents concomitantly.[44] Hence, it suggested that the availability on the market of new classes of drugs such as meglitinides and thiazolidinedione have expanded the possibility of personalizing therapy to achieve better glucose control in patients whose glycaemia is not controlled by a single agent.[44] A study done by UKPDS Group showed that the early progression to combination therapy can help maintain better blood glucose control than that which can be achieved with single agents.[45] In contrary to this, a study done by Garber, et al, found that majority of the patients had received monotherapy.[46] According to Bennett, et al., the combinations of two drugs compared with monotherapy had additive effects, in terms of not only improved glycemic control but also risk for adverse events and weight gain.[25] A UKPDS has also demonstrated that the combination of various drugs improved the levels of HbA1c, though it has not been investigated in

this study.[45] According to previous studies, the reason for this uncontrolled glycaemia may be a consequence of progressive loss of β-cell function or deterioration of insulin resistance which is caused by persistent hyperglycemia and development of resistance to the drug.[47,48] This might also be the plausible explanation for not having significant association between duration of use of medications and glycemic control in this study. Such evidence warrants the emergence of a close monitoring and aggressive treatment to achieve the therapeutic goal.

Glycemic control in DM2 patients is a huge challenge despite the discovery of novel drugs as well as new insight into the pathophysiology of the disease. So, we attempted to relate various factors which might have association with the glycemic control.

In this study, irrespective of various age groups, most of the patients have uncontrolled blood glucose level. Although there is no significant relation between blood glucose control and age groups, majority of patients of > 70 years old have poor glycemic control. Various studies have shown various age groups for glycemic control.[49,50] However, we assume that with increasing age of the patients, the blood glucose control is challenging as indicated by American Diabetes Association.[50] It might be partly because of the hypothesized age-related change in the insulin sensitivity (insulin resistance) or impaired insulin secretion, rather than insulin resistance compared with their younger counterparts as suggested by previous studies.[51-53] Various age-related changes include increased adiposity, decreased physical activity, altered diet and decreased pancreatic functions.[52,53]

Uncontrolled glycemia (FBG level) was seen more in significantly higher number of women than men in our study, which is consistent to the findings of previous study.[54] In contrary, a previous study has shown no major differences in the glycemic control between men and women.[55] Similarly, prevalence of uncontrolled glycemia was different with respect to gender which varied in different populations.[56] The most important reasons for this disparity may be the social status of women in developing countries which is still poor, and the low emphasis placed on health of women.[54] Another reason for this could be that the gender differences in care, support and self-management reflects the difference in glycemic controls between men and women.[54] Previous study has shown that at ages of 35-44 years, the females are at higher risk by 60% and from ages 45 to 64 years, the rates are double than those for males.[54] Furthermore, such difference in glycemia in male and female has also been suggested to be associated with gonadal hormones levels, for instance, high testosterone levels were associated with higher risk of DM2 among women.[57]

There was no significant association between literacy, diet restriction, regular exercise and glycemic control in this study. However, these factors have been evidenced to affect the glycemic control in DM2.[32,58,59] It has been shown that diabetes prevention and control are directly related to health literacy.[58] A study has stated that greater obesity related with diet and regular exercise was associated with greater requirement for multiple therapies and that it was more difficult to achieve the target glucose level in such patients.[32] This confirms that the patient must maintain a healthy diet to prevent obesity. Exercise decreases hepatic and muscle insulin resistance and increases glucose disposal through several mechanisms hence reducing the risk of diabetic complications significantly.[59]

Our study showed that the significantly higher number of the patients who lack knowledge about the disease and medication have uncontrolled FBG level. This finding is consistent to the findings from previous study which also revealed significant association between knowledge about DM and glycemic control.[60] This may be due to several factors such as inappropriate ways of providing information and most importantly lack of time due to the huge patient loads and lack of appropriately trained support staff as suggested by previous study.[60] Diabetes education is very essential in reaching good self-management.[61] This also partly explains the reason for many patients in our study, who do not visit their treating physicians regularly to have uncontrolled glycemia. Moreover, it has also been suggested that the knowledge improvement is a necessary condition for behavior change in DM.[61] There is an alarming need for emphasizing the diabetes awareness activities in the form of mass media campaigns, public lectures and door to door campaigns on a massive scale in both urban and rural areas to maintain the glycemia under control.[61]

Majority of the patients enrolled in our study reported of taking their medication by themselves and most of them have poor glycemic control though the association was not statistically significant. Even, the patients who claimed of having social support had uncontrolled blood glucose level in this study. This concurs well with the previous studies which have suggested that family or social group members are likely to create confusion in patients regarding their medication taking pattern because of their divergent views on patients illness and treatment, as a result of which, poor medication adherence is assured resulting into poor clinical outcomes.[62,63] However, other studies have found that patients receiving social support had better clinical outcomes because of better medication adherence.[64,65] Furthermore, in contrast to the previous studies which showed significant association between medication affordability and glycemic control, our study did not show such association.[66] Such contrasting results might be due to the involvement of a relatively small patient population and lack of follow-up period. Nevertheless, the relationship between various confounding factors and health outcomes in DM2 patients cannot be overruled in the present scenario. So this study addresses the need of further prospective studies to explore more about the association of glycemic control and various confounding factors.

CONCLUSION

Our study showed that the most commonly prescribed drug as monotherapy was biguanides and as combination therapy, biguanides and sulphonylureas were frequently prescribed. A significant association was found between FBG level and gender, knowledge about disease and knowledge about medication. Our findings warrant the need of committed initiatives and interventions to overcome the poor glycemic control.

REFERENCES

1. Zimmet P, Alberti KGMM, Shaw S. Global and societal implications of the diabetes epidemic. *Nature.* 2001; 414: 782–7.

2. Wild S, Roglic G, Grees A, Sicree R, King H. Global prevalence of diabetes. Estimates for the 2000 and projection for 2030. *Diab Care.* 2004;27: 1047–53.

3. IDF Diabetes Atlas: country estimates table 2011. 2012. [cited 2019 November 01] Available from: http://www.idf.org/sites/default/.

4. Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. *The Lancet.* 2007 Dec 14; 370(9603):1929-38.

5. Bloomgarden ZT. Type 2 diabetes in the young. *Diab Care.* 2004 Apr 1;27(4):998-1010

6. U.K. Prospective Diabetes Study (UKPDS) Group U.K. Prospective Diabetes Study 16: overview of six years' therapy of type 2 diabetes: a progressive disease. *Diabetes.* 1995; 44: 1249-58.

7. Riddle MC. Timely initiation of basal insulin. *The American journal of medicine.* 2004 Feb 2;116(3):3-9.

8. Turner RC, Cull CA, Frighi V, Holman RR. UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *Jama.* 1999 Jun 2;281(21):2005-12.

9. Ogden CL, Carroll MD. Prevalence of overweight, obesity, and extreme obesity among adults: United States, trends 1960–1962 through 2007–2008. *National Center for Health Statistics.* 2010 Jun;6(1):1-6.

10. Sclavo M. Cardiovascular risk factors and prevention in women: similarities and differences. Italian heart journal. *Supplement: official journal of the Italian Federation of Cardiology.* 2001 Feb;2(2):125-41.

11. Abdelmoneim I, Al Homrany MA. Health education in the management of diabetes at the primary health care level: is there a gender difference? 2002

12. Rhee MK, Cook CB, El-Kebbi I, Lyles RH, Dunbar VG, Panayioto RM, Berkowitz KJ, Boyd B, Broussard S, George CD. Barriers to diabetes education in urban patients' perceptions, patterns, and associated factors. *The Diabetes Educator.* 2005 May;31(3):410-7.

13. Karki P, Baral N, Lamsal M, Rijal S, Koner BC, Dhungel S, Koirala S. Prevalence of non-insulin dependent diabetes mellitus in urban areas of eastern Nepal: a hospital based study.

14. Shrestha UK, Singh DL, Bhattarai MD. The prevalence of hypertension and diabetes defined by fasting and 2-h plasma glucose criteria in urban Nepal. *Diabetic Medicine.* 2006 Oct 1;23(10):1130-5.

15. Chhetri MR, Chapman RS. Prevalence and determinants of diabetes among the elderly population in the Kathmandu Valley of Nepal. *Nepal Med Coll J.* 2009 Mar;11(1):34-8.

16. Cline MS, Smoot M, Cerami E, Kuchinsky A, Landys N, Workman C, Christmas R, Avila-Campilo I, Creech M, Gross B, Hanspers K. Integration of biological networks and gene expression data using Cytoscape. *Nature protocols.* 2007 Oct 1;2(10):2366-82.

17. Group UP. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ: British Medical Journal.* 1998 Sep 12:713-20.

18. Kalra S, Jena BN, Yeravdekar R. Emotional and Psychological Needs of People with Diabetes. *Indian J Endocrinol Metab.* 2018 Sep-Oct;22(5):696-704.

19. Peveler RC, Bryden KS, Neil HA, Fairburn CG, Mayou RA, Dunger DB, et al. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. *Diabetes Care.* 2005;28:84–8.

20. Holman R. Metformin as first choice in oral diabetes treatment: the UKPDS experience. *Journeesannuelles de diabetologie de l'Hotel-Dieu.* 2007:13-20.

21. Mazzaglia G, Yurgin N, Boye KS, Trifirò G, Cottrell S, Allen E, Filippi A, Medea G, Cricelli C. Prevalence and antihyperglycemic prescribing trends for patients with type 2 diabetes in Italy: a 4-year retrospective study from national primary care data. *Pharmacological research.* 2008 May 31;57(5):358-63.

22. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. *Diabetes.* 1985 Mar 1;34(3):222-34.

23. Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. *Diabetes Care.* 1995 Mar 1;18(3):307-14.

24. Dashputra AV, Badwaik RT, Borkar AS, Date AP, Kalnawat NR. Pattern of antidiabetic drugs used in outpatient and hospitalized patients in a tertiary health institute of central India. *Hypertension.* 2014;89(59.3):68.

25. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Annals of internal medicine.* 2011 May 3;154(9):602-13.

26. Lupi R, Del Guerra S, Fierabracci V, Marselli L, Novelli M, Patanè G, et al. Lipotoxicity in human pancreatic islets and the protective effect of metformin. *Diabetes.* 2002 Feb 1;51(suppl 1): S134-7.

27. Bailey CJ. Biguanides and NIDDM. *Diabetes care.* 1992 Jun 1;15(6):755-72.

28. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Annals of internal medicine.* 2002 Jul 2;137(1):25-33.

29. DeFronzo RA, Goodman AM, Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *New England Journal of Medicine.* 1995 Aug 31;333(9): 541-9.

30. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, et al. Risk of cardiovascular disease and all-cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *Bmj.* 2009 Dec 4;339: b4731.

31. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ.* 2005 Jun 2;330(7503):1304-5.

32. Turner RC, Hattersley AT, Shaw JT, Levy JC. Type II diabetes: clinical aspects of molecular biological studies. *Diabetes.* 1995 Jan 1;44(1): 1-0.

33. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes. *Diabetes care.* 2004 Jan 1;27(1):17-20.

34. Tosh SM, Brummer Y, Wolever TM, Wood PJ. Glycemic response to oat bran muffins treated to vary molecular weight of β-glucan. *Cereal Chemistry.* 2008 Mar;85(2):211-7.

35. Riddle MC. Timely initiation of basal insulin. *The American journal of medicine*. 2004 Feb 2;116(3):3-9.

36. Tanaka K, Nishide J, Okazaki K, Kato H, Niwa O, Nakagawa T, et al. Characterization of a fission yeast SUMO-1 homologue, pmt3p, required for multiple nuclear events, including the control of telomere length and chromosome segregation. *Molecular and cellular biology*. 1999 Dec 1;19(12):8660-72.

37. Polonsky WH, Zee J, Yee MA, Crosson MA, Jackson RA. A community-based program to encourage patients' attention to their own diabetes care. *The Diabetes Educator*. 2005 Sep;31(5):691-9.

38. Kilbourne AM, Reynolds CF, Good CB, Sereika SM, Justice AC, Fine MJ. How does depression influence diabetes medication adherence in older patients?. *The American Journal of Geriatric Psychiatry.* 2005 Mar 31;13(3):202-10.

39. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6. 2 mutations. *New England Journal of Medicine.* 2006 Aug 3;355(5):467-77.

40. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. *Diabetes Care.* 1989 Mar 1;12(3):203-8.

41. Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994-2007. *Archives of internal medicine.* 2008 Oct 27;168(19):2088-94.

42. Cosson E, Pham I, Valensi P, Pariès J, Attali JR, Nitenberg A. Impaired coronary endothelium–dependent vasodilation is associated with microalbuminuria in patients with type 2 diabetes and angiographically normal coronary arteries. *Diabetes care.* 2006 Jan 1;29(1):107-12.

43. Birkeland KI, Rishaug U, Hanssen KF, Vaaler S. NIDDM: a rapid progressive disease Results from a long-term, randomised, comparative study of insulin or sulphonylurea treatment. *Diabetologia.* 1996 Nov 1;39(12):1629-33.

44. Baviera M, Cortesi L, Tettamanti M, Avanzini F, Marelli G, Marzona I, et al . Changes in prescribing patterns and clinical outcomes in elderly diabetic patients in 2000 and 2010: analysis of a large Italian population-based study. *European journal of clinical pharmacology*. 2014 Aug 1;70(8):965-74.

45. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The lancet.* 1998 Sep 12;352(9131): 837-53.

46. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, et al. LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *The Lancet.* 2009 Feb 13;373(9662):473-81.

47. Olefsky JM, Kolterman OG, Scarlett, JA:Insulin action and resistance in obesityand noninsulin-dependent type II diabetesmellitus. *Am J Physiol.* 1982;243:E15–E30.

48. Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, et al. Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. *Journal of Clinical Investigation*. 1989 Jul;84(1):205.

49. Bozkaya G, Ozgu E, Karaca B. The association between estimated average glucose levels and fasting plasma glucose levels. *Clinics*. 2010;65(11):1077-1080.

50. American Diabetes Association. Standards of medical care in diabetes 2013. *Diabetes Care*. 2013; 36(Suppl 1):S11–66.

51. Chen M, Bergman RN, Pacini G, Porte Jr D. Pathogenesis of age-related glucose intolerance in man: insulin resistance and decreased β-cell function. *The Journal of Clinical Endocrinology & Metabolism*. 1985 Jan 1;60(1):13-20.

52. Xiao J, Weng J, Ji L, et al. Worse beta-cell function and better insulin sensitivity in older Chinese without diabetes. *J Gerontol A Biol Sci Med Sci.* 201310.1093/gerona/glt104

53. Gunasekaran U, Gannon M. Type 2 diabetes and the aging pancreatic beta cell. *Aging (Albany NY).* 2011; 3:565–575.

54. Shrestha AD, Kosalram K, Gopichandran V. Gender difference in care of type 2 diabetes. *Journal of the Nepal Medical Association*. 2013 Jan 1;52(189).

55. Kortum E, Leka S, Cox T. Psychosocial risks and work-related stress in developing countries: health impact, priorities, barriers and solutions. *International journal of occupational medicine and environmental health.* 2010 Jan 1;23(3):225-38.

56. Hilawe EH, Yatsuya H, Kawaguchi L, Aoyama A. Differences by sex in the prevalence of diabetes mellitus, impaired fasting glycaemia and impaired glucose tolerance in sub-Saharan Africa: a systematic review and meta-analysis. *Bulletin of the World Health Organization* 2013;91:671-682D.

57. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *Jama.* 2006 Mar 15;295(11):1288-99.

58. Qin L, Xu H. A cross-sectional study of the effect of health literacy on diabetes prevention and control among elderly individuals with prediabetes in rural China. *BMJ Open.* 2016;6:e011077. doi: 10.1136/bmjopen-2016-011077

59. Ivy JL, Zderic TW, Fogt DL. Prevention and Treatment of Non-Insulin-Dependent Diabetes Mellitus. *Exercise and sport sciences reviews*. 1999 Jan 1;27(1):1-36.

60. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, et al. Diabetes Epidemiology Study Group in India (DESI. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia*. 2001 Sep 1;44(9):1094-101.

61. Mohan D, Raj D, Shanthirani CS, Datta M, Unwin NC, Kapur A, et al. Awareness and knowledge of diabetes in Chennai-the Chennai urban rural epidemiology study [CURES-9]. *Japi.* 2005 Apr 1;53:283-7.

62. Myers RE, Chodak GW, Wolf TA, Burgh DY, McGrory GT, Marcus SM, et al. Adherence by African American men to prostate cancer education and early detection. *Cancer.* 1999 Jul 1;86(1):88-104.

63. Straughan PT, Seow A. Attitudes as barriers in breast screening: a prospective study among Singapore women. *Soc Sci Med*. 1982.2000 Dec;51(11):1695-703.

64. Taal E, Rasker JJ, Seydel ER, Weigman O. Health status, adherence with health recommendations, self-efficacy and social support in patients with rheumatoid arthritis. *Patient Educ Couns*.1993;20(2):63-76.

65. Svensson S. Medication adherenc, side effects and patient-physician interaction in hypertension. [Goteberg]: Department of Clinical Pharmacology, Institute of Internal Medicine, The Sahlgrenska Academy at Goteberg University; 2006.

66. Abdulganiyu G, Fola T. Poverty, Affordability of Anti-Diabetic Drugs and Glycemic Control: An Unholy Alliance in a Developing Economy? *International Journal of Pharma Sciences and Research (IJPSR)*. 2013; 4:113-20.