

Factors Responsible for Delay in Initiation of Insulin Treatment in Type-2 Diabetes Mellitus Patients with Secondary Failure of Oral Hypoglycemic Agents

Muhammad Mujeeb Khan ¹, Shehzad Manzoor ², Mohammad Ali Khalid ³, Maliha Gull Tarrar ⁴, Faiza Aslam ⁵, Syed Irfan Ahmed ⁶

1.Department of Infectious Diseases ,Holy Family Hospital and Rawalpindi Medical College;2. Department of Medicine, Benazir Bhutto Hospital and Rawalpindi Medical College;3. Department of Medicine,Benazir Bhutto Hospital and Rawalpindi Medical College;4. Department of Social Work, University of Sargodha.;5. Department of Medical Education, Rawalpindi Medical College, Rawalpindi;6.Department of Medicine, Islamabad Medical and Dental College, Islamabad

Abstract

Background: To assess patients' and physicians' perceptions regarding factors responsible for delay of Insulin initiation and compared.

Methods: In this cross sectional study using mixed quantitative and qualitative approach, quantitative component included structured interviews of 400 Type 2 Diabetic patients with failure to oral hypoglycemic agents (equally stratified based on gender and public or private health care settings) who had not initiated Insulin despite physicians advice. For qualitative aspect, 4 Focus group discussions with 29 consultant physicians of diabetic patients and four including 31 diabetic patients with delay were conducted. The factors responsible for delay and mean duration of delays were assessed and also compared based on gender and health care type.

Results: The mean duration of diabetes in 400 patients was 12.91±3.78 years while the duration of delay in months was 23.08±14.62 months with highly statistically significant increase in female patients. Patients identified fear of injection or needle phobia as the commonest factor (24.62%), followed by fear of side effects of Insulin (18.87%). Consultant physicians in addition to same above factors also mentioned the role of quacks and fear of loss of patients by doctors as important factors.

Conclusion: Factors identified by patients and physicians responsible for delay of initiation of insulin included perceptions of fears, difficult and lifelong application, cost, storage issues, last resort of treatment, misdirection from quacks and patients reluctance tempting doctors to hold up insulin till inevitable.

Key Words: Insulin,Diabetes Mellitus Type 2, Hypoglycemic agents

Introduction

Delay in initiation of Insulin in type 2 Diabetic patients, with secondary failure of oral hypoglycemic agents, is a serious issue and may lead to early development of diabetic complication. ¹ The prevalence of diabetes in the world was 8.3% while in Pakistan it was 7.89% in 2011. ² It had shown an increase in Pakistan since 2007 when the prevalence of diabetes in the urban versus the rural areas was 6.0% in men and 3.5% in women against 6.9% in men and 2.5% in women, respectively. ³ Globally the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 and the rise is more significant in middle and low income countries. Diabetes alone was directly responsible for an estimated 1.5 million deaths in 2012. ⁴ World Health Organization projects that diabetes will be the 7th leading cause of death in 2030. ⁵ The gravity of the situation is reflected by the projected number of people with diabetes to rise from 171 million in 2000 to 366 million in 2030. ⁶ Diabetes mellitus type 2 or Type 2 diabetes makes up about 90% of cases of diabetes (remaining contributed by diabetes mellitus type 1 and gestational diabetes) and is distinguished by insulin resistance, high blood sugar and relative lack of insulin ⁷⁻¹⁰

The complications of type 2 diabetes include heart disease, stroke, diabetic retinopathy which can result in blindness, kidney failure, and even amputations. ⁷ There is a need to timely prevent, diagnose and manage type 2 diabetes. Its recommended management include trial of diet and exercise but in case of failure to attain normal glycemic control within a three-month period with both, pharmacological intervention in the form of oral hypoglycemic agents is required. ¹¹⁻¹³ With progressive disease, in type 2 diabetes patients diminished insulin secretion due to declining β -cell function eventually leads to

uncontrolled glycemic control even with oral agents and most patients need treatment with exogenous insulin at some point during their lifetimes.¹⁴⁻¹⁶ The effectiveness of early progression to insulin has not only resulted in attainment of good glycemic control but also prevents complications.¹⁷⁻¹⁹

In spite of evidence of effectiveness, the common practice is that Diabetic patients are reluctant to initiate Insulin therapy.²⁰ It is a common practice to observe delay in initiation even in developed countries as study in UK showed that 25% of patients with Type 2 diabetes had insulin initiation delayed for at least 1.8 years, and 50% of patients delayed starting insulin for almost 5 years after failure of glycaemic control even in the presence of diabetes-related complications.²¹ Various qualitative studies have identified common barriers directing the type 2 diabetic patients to delay initiation of Insulin were related to negative concerns and beliefs related to Insulin like as fear of Injection, needle phobia, pain, inconvenience, embarrassment, lifestyle restriction, social stigma, and poor self-efficacy, prolonged treatment period, hypoglycemia, difficult technique.²²⁻³⁰ Unfortunately the delay is not only attributed to patients alone, research has shown that even health care providers also have contributed to this delay in initiating Insulin in type 2 patients, in spite of clinical requisite, due to their attitude and difficulty in explaining and training patients regarding Insulin.^{31,32}

Patients and Methods

This cross sectional study, using mixed quantitative and qualitative approach was conducted in Rawalpindi from November 2014 to February 2016 . Study population comprised of type -2 diabetes mellitus patients , with ages above 40 years and who in spite of advice by the Medical consultant to initiate Insulin (due to secondary failure of hypoglycemic agents) had not initiated Insulin since advice. All the pregnant women or those diagnosed as cases of gestational diabetes and type-2 diabetic patients having any acute surgical problem, severe infections or any condition for which they were advised to initiate Insulin temporarily by the doctors i.e. other than, secondary failure of hypoglycemic drugs were excluded. Patients admitted or advised admissions in the indoor department of facilities were also not included. The patients were selected from Benazir Bhutto Hospital and from two private diabetic centers. The qualitative paradigm of the study embraced the assessment of the perspectives of health care providers(n=29). Medical consultants having at least 10 years of clinical experience of diagnosing and

managing type 2 diabetes patients) regarding the factors responsible for delay in initiation of insulin therapy by patients of type 2 diabetes with secondary failure to oral hypoglycemic agents both on part of patients and the health care providers and consequences of this delay. Four Focus Group Discussions (FDG's) were conducted including 6-8 medical consultants in each, two with public health care providers and two with those practicing in private setups. Since the qualitative method was also adopted to determine the perceptions of patients themselves regarding the reasons for delay, therefore four Focus Group Discussions were also conducted with 31 diabetic patients. The selection of the participants for FDG's was made through purposeful homogenous sampling and snowball or chain sampling technique. The quantitative aspect of the study comprised of structured interviews of diabetic patients who delayed the initiation. Keeping the anticipated proportion of factors for delay as unknown (hence 50%), level of confidence 95% and absolute precision as 5%, the minimally required sample through WHO calculator was calculated to be 385, however 400 patients were included 200 from private sector and 200 from public sector, amongst each sector and patients were further stratified based on gender keeping half males and half females. The responses of interviews were then was entered and analyzed in Statistical Package of Social Sciences (SPSS). Pearson's Chi square test was applied at 5% level of significance, to compare the factors based on gender and public or private sectors. Since the numerical variables like age of patients, duration of Diabetes and duration of delays were not normally distributed, therefore Mann-Whitney U test was applied at 5% level of significance to compare their means ranks based on gender and public or private sectors.

The mean age of the study participants in years, along with duration in years since diabetes was diagnosed (duration of Diabetes) and duration in months since when they were advised to switch to insulin from oral hypoglycemic agents by their doctors for first time (duration of delay) The same variables were used to compute the mean ages of patients at which Insulin was advised for first time (present age minus duration of delay) and mean duration of diabetes in years when insulin was advised (Duration of Diabetes minus duration of delay).

Results

Statistically significant differences were observed amongst gender groups where females had higher mean values, however the variables were homogenous in public and private patients (Table 1). Majority of

patients (77.5%) confessed that they were shocked, surprised and afraid to hear about initiation of insulin (p-value 0.001). Only 35 patients (8.8%) stated that they agreed with the doctors decision of switching to insulin. Injection phobia was the commonest factor for delay in initiating insulin (Table 2).

When study participants were asked if they continued receiving treatment from the same doctors once he/she had advised them to initiate insulin treatment, (32.2%) told they stopped receiving treatment from that doctor. One hundred and sixty seven (41.8%) continued management of diabetes from same doctor on regular basis. 167 Patients, who continued regular

management from same doctors, still did not initiate insulin but had insisted their doctor to either change oral hypoglycemic agents (53.29%) or continue with their same doses with assurance of strict diet control and exercise (46.70%). 233 patients who either discontinued consultation from same doctor, or became irregular in consultations had either initiated consultation from a new doctor (57.93%), shifted to hikmat/herbal treatment (17.59%), homeopathic treatment (7.29%), spiritual healers or Aalim (5.57%), or discontinued any type of treatment and relied on exercise and diet control only (11.58%).

Table 1. Descriptive statistics of durations

Variables	All patients Mean±SD	Females Mean±SD	Male Mean±SD	p-value	Public facility Patients Mean±SD	Private facility Patients Mean±SD	p-value
Age (In Years)	60.72±6.69	62.13±6.6	59.31±6.44	***0.00	61.2±7.36	60.1±5.93	0.22
Duration of Diabetes (In Years)	12.91±3.78	13.48±3.3	12.33±4.10	***0.00	13.1±4.17	12.6±3.33	0.14
Duration of Delay (In Months)	23.08±14.62	24.6±15.1	21.48±13.91	**0.03	22.9±14.8	23.2±14.41	0.71
Age (in years) at which Insulin was advised	58.79±6.19	60.07±6.1	57.51±6.02	***0.00	59.3±6.81	58.2±5.45	0.13
Duration of Diabetes when Insulin was advised (in years)	10.98±3.66	11.4±3.43	10.54±3.84	***0.00	11.2±3.86	10.6±3.43	0.12

* Standard Deviation ** Statistically Significant ***Highly Statistically Significant

Table 2. Factors responsible for delay in initiation of insulin

Factors responsible	All	Males	Female	p-values	Public	Private	p-values
Fear of injection/needle phobia	24.62%	27.25%	22%	0.08	36.25%	13%	**0.00
Side effects like hypoglycemia weight gain, local swelling & infection	18.87%	21.75%	16%	*0.03	18.75%	19%	0.92
Difficulty in storage and transport	6%	3%	9%	**0.00	8.5%	3.5%	**0.00
Social stigma	2.37%	1.75%	3%	0.24	2.5%	2.25%	0.81
Last resort of treatment of Diabetes	2.12%	3.25%	1%	*0.02	3.25%	1%	*0.02
Painful	12.87%	7.5%	18.25%	**0.00	9%	16.75%	**0.00
Difficulty in understanding the procedure	5.37%	6.5%	4.25%	0.15	4.25%	6.5%	0.15
Difficult process of application and dosage	11.12%	13.5%	8.75%	*0.03	5.5%	16.75%	**0.00
Expensive non affordability	9.62%	5%	10.5%	**0.00	3.75%	11.75%	**0.00
No one to assist or facilitate injection	2.12%	3%	1.25%	0.08	2.25%	2%	0.80
Does not control Diabetes effectively	5.5%	6.75%	4.25%	0.12	4.75%	6.25%	0.35
No specific reason	1.25%	0.75%	1.75%	0.20	1.25%	1.25%	1.00

*Statistically Significant **Highly Statistically Significant

Table 3. Findings of focus group discussions

Perceptions of Participants of FDG's
Reasons for delay in treatment initiation
Fears: ♣ Injection or needle phobias ♣ Adverse effects like Hypoglycemia, weight gain, infections or allergic manifestations ◀ Patients absconding treatment from doctor if prescribed or insisted on Insulin initiation. Societal: ♣ Stigma and embarrassment ■ Extra burden on caregivers ■ Resistance by spouse/family members ♣ Lack of facilitation and support by caregivers. Beliefs regarding insulin: ♣ Last resort of treatment ♣ Lifelong once started/ no turning back after Insulin ♣ Anticipated ineffectiveness of Insulin. Concerns regarding application and storage: ♣ Difficulty in learning and acquiring skills to apply Insulin injection and dose adjustment ♣ Complexity of storage and transport ◀ lack of Diabetic assistants and shortage of time to explain the patients in detail the procedure of application individually and to address their concerns ■ Illiteracy Cost: ♣ Expensive ♣ lifelong expenditure ♣ Non affordability ■ Economic burden on care givers. Patients' qualms: ■ Doctors' personal gains and rewards from Pharmaceutical companies by prescribing Insulin ♣ Doctor's incompetency to attain glycemic control through oral agents. Patients' unawareness: ◀ Regarding increased risks of Diabetic complications and serious consequences if not initiated Insulin ◀ Benefits of Insulin ♣ Latest technological developments like pen Injectors. Lack of self reliance: ♣ Patients lack of confidence and self reliance regarding compliance of Insulin treatment ■ Anticipated incapability appropriate procedure of application of Injection and dose adjustment. Religious beliefs: ◀ Concerns regarding injecting medicines affecting religious rituals ◀ Strong belief in Aalims and spiritual leaders.
Consequences of delay
♣ Persistent Poor glycemic control ♣ Deterioration of glycemic control ◀ Early Development of Diabetic complications ■ Allah's will ◀ Unnecessary and continuous exposure to overdosed Oral hypoglycemic agents leading to its adverse effects ■ Nothing serious ♣ Discontinuation of current Diabetic treatment in disappointment ◀ Resort to spiritual leaders, hakims, homeopathic treatment and quakes.
Recommendations to avoid delay
◀ Awareness campaign to educate Diabetic patients regarding benefits and necessity of Insulin through media ♣ Training of appropriate procedure of application ◀ Appointment of Diabetic nurses and Diabetic educator at health care facilities for detailed counseling of Diabetic patients ◀ Strict policies against quakes claiming Insulin dangerous and attracting diabetic patients with false slogans ■ Provision of domiciliary services to inject Insulin ■ Formulation of Insulin tablets

♣ Perceptions expressed by both Diabetic Patients & Consultant Physicians ; ◀ Opinions of consultant Physicians only
 ■ Perceptions of diabetic Patients Only

Two hundred and thirty seven (59.25%) of total patients informed that their blood sugar levels had remained persistently uncontrolled since refusal to initiate insulin. In qualitative component diabetic patients shared that needle phobia was a main reason for their delay in initiation of insulin treatment (Table 3). Participants of focus group discussions, specifically

the females, were also reluctant to use it in public to avoid social rejection, embarrassment and to be considered as if suffering from a serious ailment. Some of the participants had belief that Insulin is the last option and causes hypoglycemia and weight gain. All the participants of focus group discussions were concerned about Insulin's storage and transportation issues. Many participants were not able to manage insulin treatment because of the non-cooperative attitude of care givers or not to give an extra burden to their families.

Almost all physicians were in accord that patients were reluctant to initiate insulin the instant they are prescribed for the first time and it was exceedingly rare that any patient was agreeable and keen to initiate it on first advice. Many participant consultants shared that psychological factors are the main reasons behind delay in initiation of Insulin treatment. Elderly patients were more reluctant because they resist recent technological treatments as well as lack of facilitation by their care givers. Another concern expressed by doctors was that patients receiving Insulin if ever experienced any adverse effect of Insulin he/she would exaggerate it and publicized it in a way that other relatives requiring insulin develop fear and refuse it. Few physicians belonging to private health care agreed that due to anticipated reluctance by patient, doctors keep on pending its advice as last resort, so the delay is partly contributed by doctors too.

Another issue highlighted in FDG's was of Quacks who claim to be Diabetologists through media campaign, warning diabetic patients never to take Insulin and claiming permanent treatment of Diabetes through treatment of Pancreas. Majority of consultants expressed their concerns that all the patients refusing insulin wasted their precious time due to delay in initiation and when presented again after a long period most of them had developed irreversible precarious complications of diabetes.

Discussion

Apart from the serious challenge posed by type 2 Diabetes Mellitus due to its rapid rise globally; the fact that its causation is based on intricacy of complex genetics and societal framework that determines behavior and environmental influences is also leading to serious concerns.³³ Contrary to other chronic ailments, in which the aim of management is to achieve complete cure, diabetes is at variance where the target is to maintain normal glycemic control, prevention of complications and to strive for good quality of life of patients through strict diet control,

exercise and modification in life style. Lifetime pharmacological management is an ordeal for diabetic patients who are in continuous effort to remain compliant and to handle the oscillatory doses on regular basis. After prolonged pharmacological treatment with oral hypoglycemic agents spanning over years and their failure, the news of initiation of insulin might be onerous for patients where the timing of initiation is critical and well timed start can prevent complications.

The mean duration of diabetes in our type 2 diabetic patients delaying initiation of Insulin was 12.91 ± 3.78 years, where in Japanese population it was estimated to be 10.31 years.³¹ The mean age of our patients requiring insulin initiation was 58.79 ± 6.19 years where this mean age of females was higher than males with a highly statistically significant difference. The mean period of diabetes since its diagnosis till requirement of Insulin was observed to be 10.98 ± 3.66 years, again with higher duration in female patients comparatively. This showed that not only females developed type 2 diabetes in a slightly higher age compared to men; the need to initiate Insulin was also slightly delayed in them. The mean period of diabetes since its diagnosis till requirement of Insulin is consistent with Turner RC, who concluded that 9 years after diagnosis of diabetes, majority of patients would need the addition of insulin therapy to obtain an HbA_{1c} level below 7%.³⁴ The mean duration of delay of Insulin since advised in our patients was 1.92 ± 1.21 years compared to 1.8 years projected in UK population after failure to oral agents.²¹

Majority of barriers or factor responsible for delay in initiation of Insulin from patient's perspective identified in our study are in consistency with previously conducted studies in other parts of the world.^{20-31,35} Like most of these our study also identified fear of injection or needle phobia as the commonest one (24.62%), followed by fear of side effects like hypoglycemia weight gain (18.87%), pain (12.87%) difficult procedure of application and dosage (11.12%) and expensiveness (9.62%). Social Stigma was mentioned by only 2.37% of our 400 interviewees similarly though these issues were discussed in detail but emphasized by only few in Focus group discussions, an issue perceived much important in previous studies.^{22, 24-26,35} Otherwise qualitative and quantitative paradigms of our study supported each other generally. As identified by many international studies, perception of self failure, self blame was not observed in our population.^{20,25,32,36,37}

The comparison of factors based on gender revealed, that higher number of male patients compared to females mentioned the factors regarding the side effects of the Insulin, difficult procedure of application and storage of Insulin injections and perceiving Insulin as last resort of treatment responsible, for delay in initiation. Surprisingly the fear of injection was specified more by males than females in addition to perceived ineffectiveness of Insulin and lack of facilitators for injections even though differences were not statistically significant. However, females were more concerned with issues of pain associated with Insulin injection and expensive treatment, difference being highly statistically significant compared to males, they were higher in proportion mentioning social stigma associated with Insulin. The statistically significant contrast in public and private patient's priority issues was regarding the fear of injection, difficulty of storage and last resort of treatment highlighted more by public health care patients where pain, expensiveness and difficult procedure of application were solemn apprehensions of private patients.^{27,31,32,33,35,38} Physicians did not emphasize too much on social stigma associated with Insulin coherent to findings of DAWN study.³⁵ The contribution of physicians in delay of initiation of insulin was also admitted by physicians, majority of whom belonged to private sector, as had been observed in few previous studies too, but it was more common in general practitioners and nurses.^{27,31,32, 35,39,40}

The recommendations regarding cease or prevention of delay presented by health care providers basically comprised of awareness of patients, recruitment of diabetic nurses, diabetic educators and strict policies against quacks misdirecting patients whereas suggested actions by patients were ambitious like domiciliary services and insulin tablets. The recommendations to prevent delay presented by our participants were distinctive from interventions in practice internationally except awareness and training of patients that is considered the best intervention and was valued by our participants too.^{23,24,41-46} All the patients had not initiated Insulin yet but still we did not comply with the term refusal and referred to delay because there still is optimism that they initiate it in future.

Conclusion

The imperative factors identified by patients and physicians responsible for delay of initiation of insulin in type 2 diabetic patients included fears of injection, pain and its side effects, difficult and lifelong application, cost, storage issues, last resort of

treatment, misdirection from quacks and patients reluctance tempting doctors to holdup Insulin till inevitable.

Acknowledgments

We are highly appreciative of Dr. Kamran Siddique. Public Health Consultant & Lecturer of Public Health and Professor Allan House, Professor of Liaison, Psychiatry and Director (Institute of Health Sciences and Public Health Research Nuffield Centre for International Research and Development, University of Leeds UK) for their valuable guidance and kind supervision during planning and proposal development of study.

References

1. Robert S Sherwin. Diabetes Mellitus. Cecil Text book of Medicine 22nd edition Vol 2 Elsevier Health Sciences. 2004. 1424-52.
2. Whiting DR, Guariguata L, Weil C. IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011;94:311-21.
3. Shera AS, Jawad F, Maqsood A. Prevalence of diabetes in Pakistan. *Diabetes Res. Clin. Pract.* 2007;76:219-22.
4. Global report on Diabetes. World Health Organization, Geneva, 2016
5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030.. *PLoS Med* 2006;3(11):442.
6. 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;27:1047-53.
7. "Diabetes Fact sheet N°312". WHO. January 2015. Retrieved 10 February 2016.
8. "Causes of Diabetes". National Institute of Diabetes and Digestive and Kidney Diseases. June 2014. Retrieved 10 February 2016
9. "Diabetes Fact sheet N°312". WHO. October 2013. Archived from the original on 26 Aug 2013. Retrieved 25 March 2014
10. RSSDI textbook of Diabetes Mellitus. (Rev. 2nd ed.). New Delhi: Jaypee Brothers Medical Publishers. 2012. p 235.
11. DeFronzo RA. Pharmacologic therapy for type 2 Diabetes Mellitus. *Ann Intern Med* 1999;131:281-303.
12. Feinglos MN, Bethel MA. Treatment of type 2 Diabetes Mellitus. *Med Clin North Am* 1998;82:757-90.
13. American Diabetes Association. The pharmacological treatment of hyperglycemia in NIDDM. *Diabetes Care* 1995;18:1510-8.
14. 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). *Lancet* 1998;352:837-53.
15. Wright A, Burden AC, Paisley RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 2002;25:330-36.
16. Lebovitz HE. Treating hyperglycemia in type 2 diabetes: new goals and strategies. *Cleveland Clin J Med* 2002;69:809-20.
17. Vinik A. Advancing therapy in type 2 diabetes mellitus with early, comprehensive progression from oral agents to insulin therapy. *Clin Ther* 2007;29:1236-53.
18. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus. *Diabetes Research and Clinical Practice* 1995;28(2):103-17.
19. Alvarez-Guisasola F, Mavros P, Nocea G, Alemao E.. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. *Diabetes Obes Metab* 2008;10 (1):8-15.
20. Polonsky WH and Jackson RA. What's so tough about taking insulin? Addressing the problem of psychological insulin resistance in type 2 diabetes. *Clinical Diabetes* 2004;22:147-50.
21. Rubino A, Mcquay LJ, Gough SC, Kvasz M. Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with Type 2 diabetes: a population-based analysis in the UK. *Diabetic Medicine* 2007;24(12):1412-18.
21. Phillips A. Experiences of patients with type 2 diabetes starting insulin therapy. *Nursing Standard* 2007;21(23):35-41.
22. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. *Prim Care Diabetes* 2010;1:1-8.
23. Brunton SA, Davis SN, Renda SM. Overcoming psychological barriers to insulin use in type 2 diabetes. *Clin Cornerstone* 2006;8(2):19-26.
24. Abu-Hassan H, Tohid H, Mohd Amin R. Factors influencing insulin acceptance among type 2 diabetes mellitus patients in a primary care clinic: a qualitative exploration. *BMC Fam Pract* 2013;14:164-66.
25. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy: the basis of patient reluctance. *Diabetes Care* 1997;20:292-98.
26. Lauritzen T and Scott A. Barriers to insulin therapy in type 2 diabetes: a qualitative focus group research among patients, GPs and diabetologists. *UEMO Clinical Journal* 2001;1:36-20.
27. Mollema ED, Snoek FJ, Pouwer F, Heine RJ. Diabetes fear of injecting and self-testing questionnaire. *Diabetes Care* 2000;23:765-9.
28. Mirela BP and Ha'ncu N. People with type 2 diabetes facing the reality of starting insulin therapy: factors involved in psychological insulin resistance. *Practical Diabetes Int* 2004; 21:247-52.
29. Okazaki K, Goto M, Yamamoto T, Tsujii S, Ishii H. Barriers and facilitators in relation to starting insulin therapy in type 2 diabetes. *Diabetes* 1999;48 (1):319-21.
30. Ishii H, Iwamoto Y, Tajima N. An exploration of barriers to insulin initiation for physicians in Japan: findings from the Diabetes Attitudes, Wishes and Needs (DAWN) Japan study. *PLoS One* 2012;7:e36361.
31. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005;28:2673-79.
32. Lei Chen, Magliano DJ, Zimme PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. *Nature Reviews Endocrinology* 2013;8:228-36.
33. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, Sulfonylurea, Metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA* 1999;281(21):2005-12.
34. Yoshioka N, Ishii H, Tajima N, Iwamoto Y, DAWN Japan group. Differences in physician and patient perceptions

- about insulin therapy for management of type 2 diabetes: the DAWN Japan study. *Curr Med Res Opin* 2014;30(2):177-83.
35. Polonsky WH, Fisher L, Dowe S, Edelman S, Why do patients resist insulin therapy? *Diabetes* 2003;52:A417.
36. Skovlund SE, van-Der-ven N, Pouwer F, Snoek F. Appraisal of insulin treatment in type 2 diabetes patients with and without previous experience of insulin therapy. *Diabetes* 2003;52:A419.
37. Hayes RP, Fitzgerald JT, Jacober SJ. Primary care physician beliefs about insulin initiation in patients with type 2 diabetes. *Int J Clin Pract* 2008;62(6):860-8.
38. Lakkis NA, Maalouf GJ, Mahmassani DM, Hamadeh GN. Insulin therapy attitudes and beliefs of physicians in Middle Eastern Arab countries. *Fam Pract* 2013;30(5):560-7.
39. Escalada J, Orozco-Beltran D, KMorillas CI. Attitudes towards insulin initiation in type 2 diabetes patients among healthcare providers: A survey research. *Diabetes Research and Clinical Practice* 2016;122:46-53.
40. Brod M, Alolga SL, Meneghini L. Barriers to Initiating Insulin in Type 2 Diabetes Patients: Development of a New Patient Education Tool to Address Myths, Misconceptions and Clinical Realities. *Patient* 2014;7(4):437-50.
41. Marero DG. Overcoming Patient Barriers to Initiating insulin therapy in type 2 diabetes mellitus. *Clinical Cornerstone* 2008;9(2):63-73
42. Yki-Järvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I. Initiate Insulin by Aggressive Titration and Education (INITIATE). *Diabetes Care* 2007;30(6):1364-49.
43. Simon AC, Gude WT, Holleman F, Hoekstra JB Diabetes patients' experiences with the implementation of insulin therapy and their perceptions of computer-assisted self-management systems for insulin therapy. *J Med Internet Res* 2014;16(10):e235.
44. Rosendal H, Vondeling H, de Witte LP. Initiating insulin therapy in patients with diabetes mellitus type 2: in a transmural setting is at least as effective as in an outpatient setting; a retrospective study with a 4-year follow-up. *Ned Tijdschr Geneesk* 2002;146(4):166-71.
45. Kunt T, Snoek FJ. Barriers to insulin initiation and intensification and how to overcome them. *Int J Clin Pract Suppl* 2009;(164):6-10.