



Assessment of knowledge and practice of diabetic patients towards insulin therapy

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ABSTRACT

This study was a descriptive, cross-sectional survey performed to assess knowledge and practice of diabetic patients towards insulin therapy in several diabetic centers and hospitals in Khartoum state, Sudan. The patients were interviewed and data was collected by self-administered, structured pre-tested questionnaires. The data was analysed using the statistical package for social sciences (SPSS) and Microsoft excel 2007. A total of 385 patients with type 1 or type 2 diabetes mellitus treated with insulin therapy participated in the study. 80.0% of the study participants injecting insulin in the subcutaneous tissue of thigh and upper arm while 19.2% of them inject insulin in the abdominal wall. Regarding the dose preparation, only 37.7% of the respondents appeared to know the correct way to draw insulin. Surprisingly, 82.9% of the patients knew the hypoglycemic symptoms and only 4.2% of the study participants' complaint of lipodystrophy. 78.4% of the patient's stored insulin in the refrigerator. This study explored several aspects of insulin therapy related knowledge and practice of patients and identified the need for improvement in their practices towards insulin therapy.

Keywords: Diabetes mellitus, Insulin, lipodystrophy, Drug interactions.



INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision [1]. Diabetes mellitus represents a group of diseases which has been classified into four broad clinical classes by the American Diabetes Association (ADA) as: (1) Type 1 Diabetes mellitus: Accounting for 5–10% of patients with diabetes and is characterized by pancreatic β -cell destruction usually leading to insulin deficiency [2]. (2) Type 2 Diabetes Mellitus: Accounting for 90–95% of patients with diabetes and is characterized by insulin resistance and a relative insulin deficiency [2]. (3) Gestational Diabetes: diabetes diagnosed during pregnancy [2]. (4) Other types of diabetes mellitus: Due to other causes (including genetic defects, disease of

the exocrine pancreas, and drug- or chemical induced causes) [2]. A comprehensive lifestyle intervention programme for diabetes mellitus can be defined as a programme that typically incorporates the following four main elements: medical nutritional therapy (MNT), promotion of physical activity, psychosocial care, and education. Other general healthy lifestyle interventions such as smoking cessation are also important [1]. Four principal types of insulin are available for treatment of diabetes mellitus: (1) ultra-short-acting, with very rapid onset and short duration. (2) short-acting, with rapid onset of action. (3) intermediate-acting and (4) long-acting, with slow onset of action [3]. Standard insulin regimens for managing type 1 disease vary between two to five injections daily. They must be tailored to the individual patient and will depend on lifestyle, willingness to achieve the best control and ability to cope with both injecting insulin and subsequent monitoring of blood glucose [4]. Type 2 diabetes has traditionally

been treated in a stepwise manner, starting with lifestyle modifications (medical nutrition therapy and exercise), proceeding to the use of 1 oral antidiabetic agent, followed by a combination of 2 or more oral agents before insulin is considered [5]. The importance of protecting the body from hyperglycemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type 1 and type 2 diabetes. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) [6]. Insulin may be injected into the subcutaneous tissue of the upper arm and the anterior and lateral aspects of the thigh, buttocks, and abdomen (with the exception of a circle with a 2-inch radius around the navel). Intramuscular injection is not recommended for routine injections. Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g., rotating injections systematically within the abdomen) rather than rotating to a different area with each injection [7]. The U.S. Pharmacopoeia Dispensing Information provides the following recommendations for storage of insulin vials: "An insulin bottle in use may be kept at room temperature for up to 1 month. Insulin that has been kept at room temperature for longer than 1 month should be thrown away [8].

The American Diabetes Association reminds health care professionals that even though each insulin vial is stamped with an expiration date, a slight loss of potency may occur after the vial has been in use for 30 days, especially if stored at room temperature [9]. If human insulin vials are stored under refrigeration while in use and are used beyond 30 days, the stability of these vials may be affected by a number of factors; such factors include the number of injections per day, volume of insulin remaining in the vial, exposure to light, agitation, and technique used for dose preparation. The impact of such factors is difficult to measure, and the health care professional should advise patients on an individual basis concerning long-term storage of opened insulin vials when refrigerated [9]. It was claimed that primary reasons why some patients alter their insulin intake are injection-related anxiety, concern about weight gain, and fear of hypoglycemia [10]. Injection-related anxiety, or needle phobia, is associated with higher levels of anxiety, depression, and phobic symptoms; it can result in poor glycemic control. Good communication between patient and clinician is the key in overcoming any psychological barriers to insulin therapy that some patients may have. The

optimal use of insulin therapy is dependent on the patient's intentions to use it as prescribed [10].

It was found that patients with a higher depression score rated insulin therapy significantly more negative than patients with lower depression scores. Multiple regression analyses showed that a negative appraisal of insulin therapy was significantly associated with higher depression and diabetes-distress scores and low education, but not with sex, age or duration of diabetes [11]. It was suggested that to overcome barriers to initiating insulin therapy in patients with type 2 diabetes mellitus, it's important to educate doctors on insulin initiation and the use of standardized guidelines. In addition, a patient-centered approach with better communication between doctors and patients, which may be achieved by reorganizing aspects of the health system, may improve patient knowledge, address mistaken beliefs, improve compliance and help overcome barriers [12]. It was claimed that individuals with type 1 diabetes, who have impaired awareness of hypoglycaemia, treatment with insulin lispro may be associated with a lower incidence of severe hypoglycemia manifested predominantly through less frequent nocturnal episodes. Insulin lispro may have a beneficial role in the management of patients with diabetes at risk of severe hypoglycaemia, although a larger study is required to confirm these findings [13]. One of the major barriers to insulin therapy is fear of self-injecting or fear of self-testing. Extreme levels of fear of self-injecting and/or fear of self-testing (FSI/FST) are associated with high diabetes-related distress, poor general well-being, and psychological co morbidity, as well as poorer adherence to the diabetes treatment regimen. It is concluded that patients with extreme FSI/FST are often burdened with more than this specific phobia [14]. It was found that intention to behavior was also determined by self-efficacy, e.g. expectations about the skills concerning injecting insulin. Self-monitoring of blood glucose and knowledge about diabetes positively influenced self-efficacy, attitude towards and intention to use insulin. Education needs to enforce the subjective norm and improve the patient's self-efficacy. A stimulating attitude of the treating physician towards insulin therapy is essential [15]. It was demonstrated that structured patient education improves the quality of life of diabetic patients and their metabolic control and significantly reduces the rate of acute complications [16].

Self-rated health-related quality of life (HRQL) in a group of patients is generally low. Improving diabetes knowledge and the metabolic control since early in the course of the disease, will not only retard the development of late complications, but

will certainly improve the HRQL of these patients [17]. It was demonstrated that the attitude was the most important determinant of active self-care, while a sufficient level of knowledge and a low orientation on the powerful others health locus of control scale were prerequisites for a positive attitude. The influence of the social environment was detrimental; despite the motivation of patients to active self-care, they could not provide any real help in performing this desired behavior [18]. The presence of injection related anxiety and phobia may influence compliance, glycemetic control and quality of life in patients with insulin-treated diabetes [19].

It was demonstrated that hypoglycemia is inevitable when striving for low HbA_{1c} values. Nocturnal hypoglycemia often occurs without symptoms, but results in diminished next day well-being and hypoglycemia unawareness. Frequency of nocturnal hypoglycemia was first assessed in research ward settings, but suffered from insufficient glucose sampling frequency. This may have resulted in overestimation of the duration of hypoglycemic episodes [20]. Factors that need to be considered in choosing an insulin pump include its safety features, durability of the device, tolerability and comfort of the catheter, user-friendliness, technical features and appearance. The initial insulin requirements need to be individualized for the given patient, using different methods to determine the appropriate dosages for the basal rate and prandial boluses [21]. Glycemic targets and algorithms for insulin dose adaptation need to be learned by the patients to enable them to avoid and/or correct hypo- and hyperglycemia/ketosis episodes. Patients are also advised on how to carry out frequent self-monitoring of blood glucose—and of ketone bodies, if necessary. It may be necessary to identify the reasons for lack of improvement in metabolic control after several months of therapy, which include pump malfunction, cannula problems, miscalculated insulin dosages and insufficient metabolic control in specific clinical situations with a high risk of metabolic deterioration (illness, exercise, concomitant drugs) [21].

Problem Statement and Justification: Diabetes mellitus is one of the most prevalent chronic diseases. Treatment of diabetes is a lifelong one and is important in controlling and preventing complications. Patients treated with insulin, particularly face many problems like problems of injections, storage of insulin, dose and how to take the injection. Knowledge about these aspects and about complications related to insulin or to treatment in general is essential for any diabetic patient taking insulin. This study is expected to

explore these problems and to identify gaps in knowledge and practice that need to be tackled and solved. Specific answers to these questions are expected to give key information for health care planners.

MATERIALS AND METHODS

Study design & Study area: This study is a descriptive, cross-sectional survey performed to assess knowledge and practice of diabetic patients towards insulin therapy in several diabetic centers and hospitals in Khartoum state, Sudan.

Sample size: The sample size was estimated using the following formula:

$$n = z^2 pq / d^2$$

Where n = minimum sample size z = 1.96 at 95% confidence interval obtained from standard statistical table of normal distribution p = estimated prevalence of non-adherence to guidelines in a given population (obtained from literature) q = precision i.e. prevalence of adherence in a given population (1 – p) d = margin of error (0.05) minimum sample size was found to be 385.

Data collection tool: The patients were interviewed and data was collected by self-administered, structured pre-tested questionnaires. Questionnaire consisted of both closed- and open-ended questions. In addition to questions on demographic information, the questionnaire included questions on feelings about injecting insulin, adherence to insulin injections, symptoms of hypoglycaemia and site of injecting insulin, lipodystrophy, storage of insulin and injecting technique.

Time frame: Research was started in March and was completed in June 2012.

Data analysis: The data was analyzed using the statistical package for social sciences (SPSS) and Microsoft excel 2007.

ETHICAL CONSIDERATIONS: Ethical approval was obtained from the department of research at Ministry of Health, Khartoum state, Sudan. All the patients included in the study were told about the objectives and the nature of the research. Informed consent was obtained from all patients included in the study in order to protect patient's rights of privacy and confidentiality.

RESULTS

Demographic information: The total participants included in this study were 385; 196(50.9 %) were

males and 189 (49.09%) were females (table 1). The highest percentage of diabetic patients received insulin was among the age group >50 years 234 (60.8%) (table 2) and the highest percentage of diabetic patients received insulin was among patients with primary level of education 119 (30.9%) (table 3).

Knowledge and practice of the study participants towards insulin therapy:

Injection of insulin in the Subcutaneous (SC) tissue of thigh and upper arm were the most frequent site among the study participant 311(80.8%) (table 4). 92.7% (n=357) of the patients changed their injection site and 62.3% (n=240) of the patients lack knowledge and practice towards the proper way to draw insulin therapy while 88% (n=339) of the patients knew the mechanism of injecting insulin (table 5). This study indicated that the most administered dose regimen among the patients was the twice daily regimen 74% (n=285). It appears that the unconcerned feeling regarding the daily insulin injections was the most frequent feeling among the patients 74.5% (n=287); while moderate anxiety 20.3% (n=78) and fear of injection 5.2% (n=20) (table 6). This study showed that 85.5% (n=329) of the patients administered insulin injection regularly, 82.9% (n=319) of the patients knew the hypoglycemic symptoms and only 4.2% (n=16) of the study participants complaint of lipodystrophy (table 7). This study also described the percentage of patients towards the awareness of expired date. It was found that 197(51.25%) patients were aware about the expiry date while 188(48.8%) not aware.

The percentage of patient's knowledge towards the storage place of insulin therapy:

This research indicated that refrigerator was the most commonly used area for insulin storage 78.4% (n=302); while 11.7% (n=45) of the patients stored insulin in other place such as a bottle filled with water, 7.3% (n=28) and 2.6 % (n=10) Of the patients stored insulin in the freezer and under Zeer (Zeer: manufactured locally and used to keep water) respectively.

Complications associated with diabetes among the study participants:

This study indicated that 12.5% (n=28) of the study patients had hypertension, followed by 32.5% and 10.7% had eye, and other complications (such as dental disorders, diabetic septic foot) respectively .Only 2.3% and 0.9% of the patients had renal and coronary artery disease (CAD) respectively.

Other medications received beside insulin therapy by the study participants:

It was found

that 67.8% (n=261) of the patients received other medications beside insulin therapy.

The concomitant medications included: Aspirin 141 (54%), Metformin 96 (36.8%), Atorvastatin 83(31.8%), Vitamin B1 250(19.8%), Lisinopril 44(16.9%), Amlodipine 31 (11.9%), Losartan 17 (6.5%), Glibenclamide 9(3.4%), Atenolol 9(3.4%), Pioglitazone 9(3.4%), and Thyroxin 6(2.3%) (table 9).

DISCUSSION

People with diabetes require education and support to enable them to effectively manage their disease, diet and lifestyle [4]. 80.8% (n=311) of the patients in this study had injected insulin in the subcutaneous tissue of the upper arm and thigh and only 19.2 % (n=74) of them injecting insulin in the abdominal wall. This may be due to the afraid from injection at this site. So they had administered insulin in the upper arm and thigh more frequently than abdominal wall. It reported that the abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks [7]. The study revealed that (92.7%) of the patients changed their injection site. However, most of them were lack knowledge about why they should change their injection site, they only thought that it is unlogical to inject them self at the same area continuously rather than the real cause of change i.e. lipodystrophy. Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g., rotating injections systematically within the abdomen) rather than rotating to a different area with each injection. This practice may decrease variability in absorption from day to day. Site selection should take into consideration the variable absorption between sites [9].

This study showed that 62.3% of the patients were lack knowledge about the proper way to draw insulin from the vial. Ideally the top of insulin vial should be wiped with 70% isopropyl alcohol. Then for all insulin preparations, except rapid- and short-acting insulin and insulin glargine, the vial or pen should be gently rolled in the palms of the hands (not shaken) to re- suspend the insulin. Finally the insulin vial should be taken and the equivalent amount of air to the dose should be injected to avoid creating a vacuum then the insulin should be draw into the syringe. For a mixed dose, sufficient air should be put into both bottles before drawing up the dose [7]. After the insulin is drawn into the syringe, the fluid should be inspected for air bubbles. One or two quick flicks of the forefinger against the upright syringe should allow the bubbles to escape. Air bubbles themselves are not

dangerous but can cause the injected dose to be decreased [7]. 88% of the study participants knew the route and mechanism of injecting insulin therapy. Injections are made into the subcutaneous tissue. Thin individuals or children should use short needles or may need to pinch the skin and inject at a 45° angle to avoid intramuscular injection, especially in the thigh area. Routine aspiration (drawing back on the injected syringe to check for blood) is not necessary. Particularly with the use of insulin pens, the needle should be embedded within the skin for 5 second after complete depression of the plunger to ensure complete delivery of the insulin dose [7].

The majority of patients (74%) administered insulin in the form of twice –daily regimen. Only 14.5% of the study participants did not administered insulin regularly especially the evening dose due to the fear of nocturnal hypoglycemia which occur at 3 a.m the reasons of hypoglycemia were **either** some of this category of individuals had not eaten sufficient meal before their bed time (snake) due to they did not desire to eat dinner or the food can cause stomach upset. **Or** they had received high dose of insulin therapy. This result was similar to other study which showed that the compliance of a group of patients was 74.8%, with an average of 79% in the case of a dose once daily and 38% in the case of a dose three times daily. The predominant type of noncompliance in all groups was dose omissions. However, more than one-third of the patients used more doses than prescribed. Overconsumption is a frequently made mistake by patients on a one-dose daily schedule [22].

In this study, the occurrence of lipodystrophy was examined in diabetic individuals. Only 4.2% (n=16) of the study participants complaint of lipodystrophy. This result opposed the finding in other study which showed that 48.8% of the individuals comprising the sampling established lipohypertrophy²³. The incidence of lipohypertrophy in these individuals was affected by their level of education, the frequency that they changed needles, the frequency of changing their injection sites and the amount of time they had been using insulin [23].

The study revealed that 78.4% of the patients stored insulin in the refrigerator, 2.6% of them stored it under zeer(zeer: used to store water); this may be due to their poor socioeconomic status. 7.3% stored it in the freezer ;this may be due to they lack knowledge regarding the proper storage place of insulin therapy. All insulin preparation are required to be stored in a cool and dark place, otherwise their potency is lost, as it is

temperature dependent. At 4 degree it loses only 2% potency over year, at 40 degree 2% loss occurs in one week and 5% in one month. The extremes of temperature, <2 and >30 should be avoided. The vial in current use can be safely kept at room temperature in a dark place without losing any potency, as most patients will consume it within one month. In rural areas or when refrigerator are not available, it advisable to put the vial in a plastic bag, tie a rubber band and kept in wide mouth bottle filled with water. During travel, insulin should be kept in a flask with ice or in a hand bag or proper container if outside temperature is less than 30. Insulin should never be kept in the glove compartment of a car [24]. This study was consistent with other study which concluded that insulin stored at high temperatures loses its potency and biological activity. Thus, storage in refrigerator is the ideal method of storage of insulin vials. However, when adequate storage cannot be assured at cool temperatures, insulin vials may be used within two weeks of opening [25].

This study of 385 patients with type 1 or type 2 diabetes mellitus treated with insulin had showed that 74.5% of the study participants did not avoid injections of their prescribed insulin due to anxiety or needle phobia. This result was unlike finding in other study which claimed that the primary reasons why some patients alter their insulin intake are injection-related anxiety, concern about weight gain, and fear of hypoglycemia. Injection-related anxiety, or needle phobia, is associated with higher levels of anxiety, depression, and phobic symptoms; it can result in poor glycemic control [10]. In this study 58.4% of the patients suffered from diabetic complications. 41.4% of them had more than one complication. This result was similar to finding in other study which concluded that the prevalence of diabetic complications is high among Saudi patients and many had multiple complications [26]. 12.5 %of the patients had hypertension as reported in a previous study the risk of diabetic complications in patients with type 2 diabetes was strongly associated with raised blood pressure and any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mm Hg [27]. 32.5% of the patients had eye disorders as reported in a previous study; Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for ~ 10,000 new cases of blindness every year in the United States alone. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Development of diabetic retinopathy in patients with type 2 diabetes was

found to be related to both severity of hyperglycemia and presence of hypertension in the U.K [28]. 2.3% and 0.9% of the patients had renal and coronary artery disease respectively. The percentage of such complications were low, this may be due to the size of sample were not large enough to represent this complications. As was found in a previous study the high risk of cardiovascular events observed in young patients with insulin-dependent diabetes is secondary to advanced atherosclerotic lesions in coronary arteries [29]. Also it was concluded that patients developing clinical nephropathy have a highly increased incidence of coronary heart disease compared with patients' not developing nephropathy. Patients who developed coronary heart disease were characterized by higher blood pressure and serum cholesterol [30]. The study showed that 67.8% of the patients received other medications beside insulin either for control of diabetes or for other compelling indication such as hypertension, renal problem, cardiovascular disease and atherosclerotic disease. 54% and 44% of them had administered aspirin and Lisinopril respectively. The hypoglycemic effect of insulin may be potentiated by certain drugs, such as Angiotensin converting enzyme inhibitors, salicylates (pharmacodynamics synergism). Angiotensin converting enzyme inhibitors may increase the risk of hypoglycemia by enhancing insulin sensitivity, salicylates may stimulate insulin secretion. Close monitoring for the development of

hypoglycemia is recommended if these drugs are co-administered with insulin, particularly in patients with advanced age and/or renal impairment. The insulin dosage may require adjustment if an interaction is suspected [31]. Some patients in this study also received Atorvastatin (31.8%), Amlodipine (11.9%), Metformin (36.8%), Vitamin B12 (19.8%), Losartan (6.5%), Glibenclamide (3.4%), Atenolol (3.4%), Pioglitazone (3.4%) and thyroxin (2.3%) and there were no significant interactions between insulin and these drugs [31].

CONCLUSION

According to this study it was concluded that the majority of the study participants injecting insulin in the subcutaneous tissue of thigh and upper arm. Also most of them changed their injection site. However, most of the patients lack knowledge and practice towards the proper way to draw insulin. Surprisingly, most of the patients knew the hypoglycemic symptoms and few of them complaint of lipodystrophy. This study explored several aspects of insulin therapy related knowledge and practice of patients and identified the need for improvement in their practices for insulin.

Conflict of interest: None to declare.

Table 1: indicates the frequency and percentage of patients received insulin therapy in both genders.

Gender	Male	Female	Total
% of the patient	196 (50.9%)	189 (49.09%)	385

Table 2: shows the frequency and percentage of diabetic patients received insulin in relation to different age groups.

Range of age	<20	21-29	30-39	40-49	>50
% of patients	30 (7.8%)	27 (7.1%)	39 (10%)	55 (14.3%)	234 (60.8%)

Table 3: shows the frequency and percentage of diabetic patients who received insulin in relation to different education level.

Education status	Literacy	Pre-school	primary	Secondary	university	Post-graduate
% of patients	80 (20.8%)	3 (0.8%)	119 (30.9%)	106 (27.6%)	65 (16.9%)	12 (3%)

Table 4: shows the frequency and percentage of patients towards the different site of insulin injection.

	Subcutaneous (SC) tissue of thigh and arm	Abdominal wall	Total
Site of injection	311 (80.8%)	74 (19.2%)	385

Table 5: Shows the percentage of patient's knowledge and practice towards; injection site change, preparations of dose, mechanism of injecting insulin therapy.

	Yes	No	Total
injection site change	357(92.7%)	28(7.3%)	385
preparations of dose	145(37.7%)	240(62.3%)	385
mechanism of injecting insulin	339(88%)	46(12%)	385

Table 6: indicates the percentage of patient's feeling regarding insulin injections.

	Unconcerned	Moderate anxiety	Fear of injection	Total
Patient's feeling	287(74.5%)	78(20.3%)	20(5.2%)	385

Table 7: shows the percentage of patient's awareness regards; compliance, hypoglycemic symptoms, lipodystrophy.

	Yes	No	Total
Patients' compliance	329(85.5%)	56(14.5%)	385
Hypoglycemic symptoms	319(82.9%)	66(17.1%)	385
Lipodystrophy	16(4.2%)	369(95.8%)	385

Table 8: identifies the percentage of hypoglycemic symptoms that reported among the study participants.

	Palpitation	Dizziness	Tremor	Sweating	Others
Hypoglycemic symptoms	70(22%)	87(27%)	140(43.9%)	175(54.9%)	142(44.5%)

Table 9: shows the percentage of other medications received beside insulin by the study participants.

	Aspirin	Metformin	Atorvastatin	Vitamin B12	Lisinopril	Amlodipine
% of other medications	141(54%)	96(36.8%)	83(31.8%)	50(19.8%)	44(16.9%)	31(11.9%)

Losartan	Glibenclamide	Atenolol	Pioglitazone	Thyroxine	Total
17(6.5%)	9(3.4%)	9(3.4%)	9(3.4%)	6(2.3%)	261

REFERENCES

- 1- American Diabetes Association. Diagnosis and Classification of diabetes mellitus. *Diabetes Care*. 2012; 35(7):64-71.
- 2- Schwellnus MP et al. Healthy lifestyle interventions in general practice Part 4: Lifestyle and diabetes mellitus. *SA Fam Pract*. 2009;51(1):19-25.
- 3- Umesh M, John H. Diabetes mellitus and Hypoglycemia. In: Lawrence M .Tierney, Jr, Stephen J.McPhee , Maxine A. Papadakis. *Current medical diagnosis and treatment*. 42nd ed. New York:Lange Medical Books/McGraw-Hill ,2003; pp.1152-1198.
- 4- Elizabeth A. Hackett, Stephen M. Thomas. *Diabetes mellitus*.In:Walker R, Whittlesea C. *Clinical pharmacy and Therapeutics*. 4thed. London: Churchill Livingstone, 2007; pp.629-655.
- 5- Riddle MC. Tactics for type II diabetes. *EndocrinolMetabClin North Am*.1997; 26:659-677.
- 6- Michael J F. Microvascular and macrovascular complications of diabetes. *Clinical Diabetes* 2008; 26(2):77-82.
- 7- American Diabetes Association. Insulin Administration. *Diabetes Care* 2002; 25:12-15.
- 8- United States Pharmacopoeia Dispensing Information: *Advice for the Patient*.US Pharmacopoeia Convention 2000; 2:835-836.
- 9- American Diabetes Association. Insulin administration (position statement).*Diabetes Care* 2003; 26(1):121-124.
- 10- Nada L S. Overcoming Psychological Barriers in Insulin Therapy.*Insulin*2006; 1:38-45.

- 11- Makine C et al. Symptoms of depression and diabetes-specific emotional distress are associated with a negative appraisal of insulin therapy in insulin-naïve patients with Type 2 diabetes mellitus. A study from the European Depression in Diabetes [EDID] Research Consortium. *Diabetic Medicine* 2009; 26(1): 28–33.
- 12- Monirul H et al. Barriers to initiating insulin therapy in patients with type 2 diabetes mellitus in public-sector primary health care centres in Cape Town. *South Africa Medical journal* 2005; 95(10):798-802.
- 13- Stewart C F et al. Severe hypoglycemia in patients with type 1 diabetes and impaired awareness of hypoglycemia: a comparative study of insulin lispro and regular human insulin. *Diabetes/ Metabolism Research and Review* 2001; 17:285–291.
- 14- Mollema ED et al. Insulin-treated diabetes patients with fear of self-injecting or fear of self-testing psychological comorbidity and general well-being. *Journal of Psychosomatic Research* 2001; 51(5): 665-672.
- 15- Bruce HR et al. Determinants of injecting insulin in elderly patients with type II diabetes mellitus. *Patient Education and Counseling* 1993; 22(3):117-125.
- 16- Tankova G et al. Education of diabetic patients— a one year experience. *Patient* 2001; 43(2): 139–145.
- 17- Murtada N E et al. Health-related quality of life in insulin-treated diabetic patients in the Sudan. *Diabetes Research and Clinical Practice* 1999; 46:65-73.
- 18- Inge de W et al. Determinants of active self-care behaviour of insulin treated patients with diabetes: Implications for diabetes education. *Social Science and Medicine* 1990; 30 (5):605-615.
- 19- Andrew Z et al. Injection related anxiety in insulin-treated diabetes. *Diabetes Research and Clinical Practice* 1999; 46(3): 239-246.
- 20- DeVries JH et al. Nocturnal hypoglycaemia in type 1 diabetes--consequences and assessment. *Diabetes/Metabolism Research and Reviews* 2004; 20(2):43-46.
- 21- Jeandier N et al. Treatment of Diabetes Mellitus using an external insulin pump in clinical practice. *Diabetes & Metabolism* 2008; 34(4) 425-438.
- 22- Arsenio H P et al. Impact of Dosage Frequency on Patient Compliance. *Diabetes Care* 1997; 20 (10):1512-1517.
- 23- Bahar V , Sevgi K. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. *Diabetes Research and Clinical Practice* 2007; 77(2):231-236.
- 24- American Diabetes Association. Insulin Administration. *Diabetes Care* 1999; 22: 83-86.
- 25- Vimalavathini R, Gitanjali B. Effect of temperature on the potency & pharmacological action of insulin. *Indian Journal of Medical Research* 2009; 130(2):2833-2834.
- 26- Al-Wakeel JS et al. Microvascular and macrovascular complications in diabetic nephropathy patients referred to nephrology clinic. *Saudi J Kidney Dis Transpl* 2009; 20(1):77-85.
- 27- Adler A et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes. *BMJ* 2000; 321(7258):412-9.
- 28- Michael J F. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes* 2008; 26(2):77-82.
- 29- Valsania P et al. Severity of coronary artery disease in young patients with insulin-dependent diabetes mellitus. *Am Heart J* 1991; 122(3 Pt 1):695-700.
- 30- Jensen T et al. Coronary heart disease in young Type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. *Diabetologia* 1987; 30(3):144-148.
- 31- Medscape. Interaction Checker. Available from <http://reference.medscape.com/drug-interactionchecker>. [accessed on 19/07/2012].