Role of Continuous glucose monitoring system In optimizing glucose level in patients With type 1 diabetes mellitus

Thesis

Submitted for partial Fulfillment
Of the MD Degree in Pediatrics

Presented By

Mohamed Mohamed Ismail
Msc.(Degree in Pediatrics -Cairo university 2005)

Supervisors

Prof. Dr. Nermin Salah Eldein

Professor of pediatrics
Faculty of medicine - Cairo University

Prof Dr. Mona Mamdooh

Professor of pediatrics
Faculty of medicine - Cairo University

Trof Dr. Ghada Anwar

Professor of pediatrics
Faculty of medicine - Cairo University

Pediatric Department
Faculty of Medicine
Cairo University

2010

ACKNOWLEDGEMENT

First and principal thanks are to **Allah**, the most Beneficent, Forgiving and Merciful.

I wish particularly to thank my head-supervisor **Prof. Dr. Nermine Salah,** Professor of Pediatrics,

Faculty of Medicine, Cairo University for her scholarly advice, infinite efforts, realistic support and helpful suggestions.

I would also like to convey my warm gratitude to **Prof. Dr. Mona Mamdouh,** Professor of Pediatrics,

Faculty of Medicine, Cairo University, who gave me invaluable clinical help and so useful support.

I wish also to express my thanks to **Prof. Dr. Ghada Anwar,** Professor of Pediatrics, Faculty of Medicine, Cairo University, for her kind support.

Finally I am so grateful to my parents for their support and to my **wife** and **my young** child for the serenity and forbearance.

ABSTRACT

The study could also compare the value of different therapeutic maneuvers. Splitting the evening dose provides better glycemic control with less hypoglycemia. Delaying night basal (after the midnight) showed less incidence of morning hypoglycemia.

KEY WORDS

Role _ monitoring _ patients

Table of contents

	Page				
Introdu	Introduction and aim of the work $\underline{1}$				
Review	of medical literature	6			
I.	Diabetes mellitus	6			
II.	Acute complications of type 1 diabetes	18			
	mellitus				
III.	Long term complications of type 1	26			
	diabetes mellitus				
IV.	Importance of tight glucose control	32			
V.	Methods of insulin administration	43			
VI.	Optimizing glycemia in Type1diabetes	52			
	mellitus				
VII.	Continuous Glucose Monitoring System (a	64			
	significant advance in diabetes care)				
VIII.	Diabetes care in type 1 diabetes mellitus	97			
Patients	106				
Results		124			
Discussi	170				
Conclus	195				
Summai	199				
Referen	202				
Append	230				

List of tables

No. of		Title	Page
table			
Table (1)	:	Autoimmune diseases associated with	7
		type 1 diabetes mellitus	
Table (2)	:	Differential diagnosis of diabetes mellitus	9
Table (3)	:	Absolute risk for type 1 diabetes mellitus	12
		according to DR/DQ genotypes	
Table (4)	:	Over all glycemic control of all patients	131
Table (5)	:	The average of pre-prandial and	132
		postprandial blood glucose by CGMS	
Table (6)	:	Hypoglycemias according to the duration	134
Table (7)	:	Relation of duration of hypoglycemia to	135
		age, sex, BMI, HbA1C and insulin dose	
Table (8)	:	Relation of duration of hyperglycemia to	137
		different variables	
Table (9)	:	Comparison between the frequency of	137
		hypoglycemias and hyperglycemias	
		before adjustment and after CGMS	
		based adjustment	
Table (10)	:	Average HbA ₁ c, before adjustment, 3	152
		month and 6 months after adjustment	
Table (11)	:	Comparison between 3 dose regimen and	156
		4 dose regimen group	
Table (12)	:	Group with delayed night basal insulin	159

Table (13):	Group with no delay in the night basal insulin	159
Table (14):	Comparison between the 2 groups with and without delayed night basal insulin.	160
Table (15):	Comparison between group with and without splitting the evening dose.	162
Table (16):	Comparison between patients using Glargine and patients using NPH as basal insulin.	163
Table (17):	Comparison of the 2 groups (Group with a mean change $< 45 \text{ mg/dl}$ and Group with a mean change $\geq 45 \text{ mg/dl}$).	166
Table (18) :	Comparison between patients with hypoglycemia awareness and hypoglycemia unawareness	168

List of figures

No. of		Title	Page
Figure			
Figure (1)	:	HLA regions on chromosome 6	11
Figure (2)	:	Progression of beta cell damage and	15
		the genetic risk of type 1 diabetes	
		mellitus	
Figure (3)	:	Progression to diabetes vs. number of	16
		autoantibodies (GAD, ICA512,Insulin)	
Figure (4)	:	Hypoglycemia associated autonomic	21
		failure	
Figure (5)	:	Diabetic retinopathy	27
Figure (6)	:	Diabetic neuropathy	28
Figure (7)	:	Cumulative incidence of neuropathy	34
		associated with type 1 diabetes	
		mellitus	
Figure (8)	:	Open loop system	47
Figure (9)	:	MiniMed Gold CGMS	71
Figure (10)	:	MiniMed Sensor inserted in the	72
		subcutaneous tissue	
Figure (11)	:	Automatic insertion of the Sen-serter	88
Figure (12)	:	Manual insertion of the Sen-serter	89
Figure (13)	:	CGMS sensor insertion for one of the	114
		patients	

Figure (14)	:	Percentage of patients according to the type of basal insulin used	125
Figure (15)	:	Percentage of patients according to the number of insulin injections	125
Figure (16)	:	CGMS curve matched efficiently with (SMBG) during hypoglycemia	129
Figure (17)	:	CGMS curves matched efficiently with (SMBG) during hyperglycemia	129
Figure (18)	:	The pre-prandial and the postprandial glucose levels by CGMS	132
Figure (19)	:	Percentage of day time vs. night time hypoglycemia	133
Figure: (20)	:	Classification of hypoglycemia according to the duration of the attacks	135
Figure (21)	:	Timing of the hyperglycemic attacks	
Figure (22-a)	:	CGMS curves showing recurrent attacks of postprandial hyperglycemia in 5 patients (a- b- c-d-e)	138
Figure (22-b)	:		139
Figure (22-c)	:		139
Figure (22-d)	:		140
Figure (22-e)	:		140
Figure (23-a)	:	CGMS curve showing rapid glycemic excursions in 2 patients (a-b)	141

Figure (23-b)	:		141
Figure (24)	:	CGMS curve showing postprandial hypoglycemia	142
Figure (25)	:	CGMS curve showing rebound phenomenon	142
Figure (26)	:	CGMS curve showing recurrent attacks of night time hyperglycemia	143
Figure (27-a)	:	CGMS curve showing hyperglycemic pattern in 2 patients (a-b)	144
Figure (27-b)	:		144
Figure (28-a)	:	CGMS curve showing hypoglycemic pattern in 2 patients (a- b)	145
Figure (28-b)	:		145
Figure (29-a)	:	CGMS curve showing rebound phenomenon in 2 patients (a-b)	146
Figure (29-b)	:		146
Figure (30)	:	The percentage of basal insulin and regular insulin doses before and after adjustment of insulin dose	147
Figure (31)	:	The percentage of therapeutic interventions applied for the patients included in the study.	149

Figure (32)	:	The number of hypoglycemic attacks detected before and 3 month after applying the therapeutic interventions	150
Figure (33)	:	The number of hypoglycemic attacks detected before adjustment and 3 months after adjustment.	151
Figure (34)	:	Effect of glycemic control guided by CGMS on HbA1	153
Figure (35)	:	Effect of glycemic control guided by CGMS on the cholesterol level.	153
Figure (36)	:	Effect of Glycemic control guided by the CGMS on the level of microalbuminuria	154
figure (37)	:	Comparison between 4 doses regimen and 3 doses regimen	157
Figure (38)	:	Comparison between the 2 groups with and without delayed night basal insulin	160
Figure (39)	:	Comparison between group with and without splitting the evening dose.	162
Figure (40)	:	Mean reduction in HbA1C in group with and without exercise program	164
Figure (41)	:	Mean HbA1c in the groups of patients with a mean change in blood glucose below or above 45 mg/dl.	166

Figure (42)	:	Mean blood glucose level in the groups of patients with a mean change in blood glucose below or above 45 mg/dl	167
Figure (43)	:	Comparison between patients with hypoglycemia awareness and hypoglycemia unawareness	169

List of Abbreviations

	LIST	OI ADDIEVIATIONS
Ab	:	Antibodies
ACE		Angiotensin enzyme inhibitor
ADA	<u> </u>	American Diabetes Association
AGA	:	Anti-gliadin antibodies
AITD	:	Autoimmune thyroid disease
BG	•	Blood glucose
BMI	:	Body mass index
CAD	•	Coronary artery disease
CGMS	:	Continuous glucose monitoring system
Cl	•	Chloride
CNS	:	Central nervous system
CSII	:	Continuous Subcutaneous Insulin Infusion
CVD	:	Cardiovascular disease
DCCT	:	Diabetes Control and Complications Trial
DirecNet	:	Diabetes Research in Children Network
DKA	:	Diabetic ketoacidosis
DM	:	Diabetes mellitus
DPT	<u>:</u>	Diabetes Prevention Trial
ENDIT	:	European nicotinamide diabetes intervention
		trial
FBG	•	Fasting blood glucose
FDA	:	Food and drug administration
GABA		Gama aminobutyric acid
GHb	:	Glycated hemoglobin
GIP	•	Gastric inhibitory peptide
GK	<u> </u>	Liver glucokinase
GLP-1	•	Glucagon-like peptide 1
Gold CGM	:	Gold continuous glucose monitoring system.
HAAF	<u>.</u>	Hypoglycemia-associated autonomic failure
Hb	:	Hemoglobin
HbA1c	:	Glycosylated hemoglobin
HCO_3^-	:	Bicarbonate
HDL	:	High density lipoproteins

HLA	:	Human leukocyte antigen
HUNS	:	Hypoglycemia unawareness syndrome
IA-2	:	Islet cell antibody
IAAS	:	Insulin auto-antibodies
ICA	:	Islet cell antigen
IIT	:	Intensive insulin therapy
ISO		International Organization for
		Standardization
kg	:	kilogram
LDL	:	Low density lipoproteins
MAD	:	Mean absolute difference
MDI	:	Multiple dose injection
mEq/L	:	Millie equivalent per liter
Mg	:	Milligram
mg/dl	:	Milligram per deciliter
MHC	:	Major histocompatibility complex
ml.Osm.	:	Millie osmol
MODY	:	Maturity onset diabetes of the young
MRBS	:	Mean random blood sugar
nA	:	Nano angstrom
NIDDK	:	National Institute of Diabetes and Digestive
		and Kidney Diseases
NPH	:	Neutral protamine Hagedorn
PBG	:	Postprandial blood glucose
RT-CGMS	:	Real time -continuous glucose monitoring system
SC	:	Subcutaneous
SD	:	Standard deviation
Sig.	:	Significant
SMBG	:	Self monitoring blood glucose
T1DM	:	Type 1 diabetes mellitus
T2DM	:	Type 2 diabetes mellitus
IDF	:	International diabetes federation
TID	:	Three injections per day
UKPDS	:	United Kingdom prospective diabetes study

Introduction and aim of the work

Type 1 diabetes (T1DM) is one of the most common diseases of childhood. Even with the recent epidemic of type 2 diabetes, T1DM still accounts for approximately 85% of all cases of diabetes in children (American Diabetes Association, 2010).

Diabetic children still have health care costs twice as high as children who don't have diabetes. On the other hand, the investment in the field of diabetes management reduces the high future costs of long term diabetes related complications (Icks et al., 2004).

Hyperglycemia is considered the primary pathogenic factor in development of micro and macrovascular complications (Nishikawa et al., 2004).

Retinopathy, neuropathy and nephropathy are the most common long term complications of diabetes mellitus (**Diabetes Control and Complication Research Group, 1993**).

Pediatric Clinics of North America recorded marked decrement in the incidence rate of diabetes related retinopathy and nephropathy in the last decade due to more efficient glycemic control (Sarah et al., 2005).

In addition, Diabetes Control and Complication Trial (DCCT), a large multicentric trial that involved 1441 patients with (T1DM) proved convincing evidence that improved glycemic control conferred a significant risk reduction for retinopathy, neuropathy and nephropathy (Diabetes Control and Complication Research Group, 1993).

Intensive insulin therapy and continuous subcutaneous insulin therapy were applied to achieve euglycemia satisfactory to prevent microvascular and macrovascular complications (Haller et al., 2005).

However, the major adverse effect of this regimen is the greatly increased risk of moderate to severe hypoglycemia (**Pickup et al., 2005**).

The experience of hypoglycemia is probably the most hated and feared consequence of (T1DM) in