

# Clinical

Practical Information for Primary Care

An Official  
Journal of the  
American  
Diabetes  
Association

# Diabetes

Middle East Edition

Volume 6 ■ Number 1 ■ Winter 2007

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# From the Editor's Desk

Few months ago we discussed in this place the existence of the so called Metabolic Syndrome based on analysis done by the ADA/EASD where their analysis indicates that too much critically important information is missing to warrant its designation as a "syndrome." Until much needed research is completed, clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the "metabolic syndrome.1

Also Richad Kahn later described it as an emperor wearing NO cloths based on the facts that metabolic syndrome as defined is associated with many uncertainties and inconsistencies, and its clinical value is highly questionable if not nonexistent. Indeed, rather than being an instrument that moves medical care in a valuable direction, it has all the qualities that could easily misdirect care, mislead patients, create uncertainty, and lead to unnecessary health care costs. For example, the cost-effectiveness and justification for stand-alone fitness and psychological counseling programs under the guise of treating a unique disease seem unclear at best. No one questions the belief that there are many Cardiometabolic risk factors that deserve attention. Being overweight or obese is one such important factor. Fortunately, we have guidelines and well-documented therapies that reduce all of these CVD and diabetes risk factors, individually or in combination, and lifestyle modification is the cornerstone of treatment. To make this paradigm any more complex seems pointless.2

Lastly and few days ago there was a study published in Diabetes Care about central obesity where the International Diabetes Federation (IDF) proposes that central obesity is an "essential" component of the metabolic syndrome, while the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) proposes that central obesity is an "optional" component. This study examines the effect of the metabolic syndrome with and without central obesity in an Asian population with ischemic heart disease (IHD).

From the population-based cohort study (baseline 1992–1995), 4,334 healthy individuals were grouped by the presence or absence of the metabolic syndrome and central obesity and followed up for an average of 9.6 years by linkage with three national registries. Cox's proportional hazards model was used to obtain adjusted hazard ratios (HRs) for risk of a first IHD event. The prevalence of metabolic syndrome was 17.7% by IDF criteria and 26.2% by AHA/NHLBI criteria using Asian waist circumference cutoff points for central obesity. Asian Indians had higher rates than Chinese and Malays. There were 135 first IHD events. Compared with individuals without metabolic syndrome, those with central obesity/metabolic syndrome and no central obesity/metabolic syndrome were at significantly increased risk of IHD, with adjusted HRs of 2.8 (95% CI 1.8–4.2) and 2.5 (1.5–4.0), respectively.

The study concluded that Having metabolic syndrome

either with or without central obesity confers IHD risk. However, having central obesity as an "optional" rather than "essential" criterion identifies more individuals at risk of IHD in this Asian cohort.3

I believe that we are still on the track that highly consider the Cardiometabolic risk factors independently rather than describing it in vague cluster called Metabolic Syndrome!

**Mahmoud Ashraf Ibrahim, MD**  
Editor, Middle East Edition

1- Richard Kahn, PHD, John Buse, MD, PHD, Ele Ferrannini, MD and Michael Stern, MD, The Metabolic Syndrome: Time for a Critical Appraisal Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes Diabetes Care 28:2289-2304, 2005

2- Richard Kahn, PHD, The Metabolic Syndrome (Emperor) Wears No Clothes, Diabetes Care 29:1693-1696, 2006.

3 - STEFAN MA, PHD, DERRICK HENG, MBBS, CHEE-ENG TAN, PHD, SUOK-KAI CHEW, MSC, KENNETH HUGHES, DM, E-SHYONG TAI, MB, CHB, JEANNETTE LEE, MBBS, Should Central Obesity Be an Optional or Essential Component of the Metabolic Syndrome? Diabetes Care 30:343–347, 2007.

## Clinical Diabetes

A PUBLICATION OF THE AMERICAN DIABETES ASSOCIATION®, INC.™

Middle East Edition, Volume 6, Number 1, 2007



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**This edition contains the full contents of the original US version, in addition to the local articles selected by the Local Advisory Board, these local articles do not appear in the US version.**

**Contact information :**

Mailing address :

19 Nasouh St., Zeitoun,  
Cairo 11321 Egypt

Telephone : +( 2010 ) 1560794

Fax : +( 202 ) 2723693

E-mail : mahmoud@arab-diabetes.com

## Abstracts of Oral Presentations, International Diabetes Conference "Global Aspects of Diabetes: Shaping the Future" 30 Oct. – 2 Nov. 2006 Kuwait Part I

### Implementation of Diabetes Care Programme Standards and Variations in Practice at the Primary Care Setting in Kuwait

Al-Adhani AMS 1, Saba W 2, Al-Jassar Sh 3, Al-Sultan F 4, El-Feky M 5, Al-Mezel N 6. 1 Diabetes Unit, Department of Medicine, Al-Sabah Hospital, 2 Al-Sulaibiya Clinic 3 Al-Nuzha Clinic, 4 South Hawalli Clinic, 5 Al-Rabiya Clinic, 6 Al-Riqqa Clinic

#### Introduction:

Diabetes Care Programme (DCP) was established in order to improve the quality of diabetes care at the Primary Health Care (PHC) Setting in Kuwait. We carried out this study to evaluate the implementation of the defined standards and to assess the variations between practices.

#### Methods:

In 2003, an audit has been conducted for 34 centers in the PHC setting that provide diabetes care services by on-site visits and medical record review. Medical records are included only if the patients had had three or more visits during the year. Several factors were included to evaluate the structure and process of diabetes care.

#### Results:

In 2003, a total of 34 centers were visited and 820 medical records were reviewed. The review revealed that of all subjects, 29 and 22% had fundus and foot examination respectively. The proportion of patients who were asked for smoking status was 19%. Of all subjects 46, 64, and 28% were tested for HbA1c, serum creatinine, and microalbuminuria respectively. The proportion of patients who were tested for triglycerides, total cholesterol, HDL-cholesterol, and LDL cholesterol was 65, 65, 24, and 21 % respectively. There were great variations in the implementation of these standards between the practices. Patients' adherence to their appointment in the practice affected positively the implementation of the following standards: smoking status, fundus examination, measurement of HbA1c, serum creatinine, HDL-, and LDL- cholesterol. Use of structured visit sheets improved the implementation of assessment of smoking status, foot examination, measurement of microalbumin, and lipid profile. Availability of fundus cameras increased fundus examination significantly. Percentage of GPs with specialized training in diabetes affected assessment of smoking status, foot examination, measurement of HbA1c and HDL-cholesterol, whereas availability of nurses in the practice affected the implementation of measurement of HDL- and LDL- cholesterol.

#### Conclusions:

Although the defined standards were implemented at the PHC setting, the quality of diabetes care is still not optimal. In addition, the great variations between the practices indicate that further interventions are needed. Strategies that improve patients' adherence to their appointment, use of structured clinical care, conducting continuous medical education programmes and addressing the role of nurses may help to improve the quality of diabetes care provided at the PHC setting in Kuwait.

### Angiotensin-(1-7) prevents diabetes-induced cardiovascular dysfunction

Benter IF 1, Yousif MH 1, Cojocel C1, Al-Maghrebi M 2, Diz D1 3 1 Department of Pharmacology & Toxicology; 2 Department of Biochemistry, Faculty of Medicine, Kuwait University; 3 The Hypertension and Vascular Disease Center, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.

#### Introduction:

Diabetes-induced cardiovascular dysfunction is evidenced clinically by accelerated atherosclerosis, retinopathy, nephropathy, occlusive vascular disease and hypertension. Alterations within the renin-angiotensin system (RAS) are considered to be important for the development of diabetic complications, particularly diabetic renal disease and hypertension. Suppression of angiotensin II (Ang II) synthesis or activity can prevent or slow

the progression of diabetes-induced cardiovascular complications. The aim of this study was to test the hypothesis that treatment with angiotensin-(1-7) [Ang-(1-7)] or Ang-(1-7) non-peptide analogue AVE0991 can produce protection against diabetes-induced cardiovascular dysfunction.

#### Methods:

We examined the influence of chronic treatment (four weeks) with Ang-(1-7) or AVE0991 on proteinuria, vascular responsiveness of isolated carotid and renal artery ring segments and mesenteric bed to vasoactive agonists, and cardiac recovery from ischemia-reperfusion (I/R) in streptozotocin (STZ)-treated rats (diabetes). Male Wistar rats weighing about 300g were used in this study. Animals were divided into six groups. Group I (control) was vehicle-treated animals. Groups II and III were control animals treated with daily intraperitoneal injection (ip) injections of Ang-(1-7) (24microg/kg/hr ip) or AVE0991 (24microg/kg/hr ip), respectively. Group IV (diabetic; D) was STZ-treated animals. Group V (D + Ang-(1-7)) and VI (D + AVE0991) were diabetic rats treated with Ang-(1-7) or AVE0991, respectively. Diabetes was induced by a single ip injection of 55mg/kg body weight STZ. Animals were sacrificed four weeks after induction of diabetes and/or treatment with Ang-(1-7) or AVE0991.

#### Results:

There was a significant increase in urine protein in diabetic animals compared to controls. Treatment of diabetic animals with Ang-(1-7) or AVE0991 resulted in a significant reduction in urine protein compared to vehicle-treated diabetic animals. Treatment with Ang-(1-7) or AVE0991 also prevented the diabetes-induced abnormal vascular responsiveness to norepinephrine (NE), endothelin-1 (ET-1), carbachol and histamine in the perfused mesenteric bed and isolated carotid and renal arteries. In isolated perfused hearts, recovery of left ventricular function from 40 minutes of global ischemia was significantly better in Ang-(1-7)- or AVE0991-treated animals.

#### Conclusions:

These results suggest that activation of Ang-(1-7)-mediated signal transduction could be an important therapeutic strategy to reduce cardiovascular events in diabetic patients. Funding Agency: Kuwait University Research Administration

### Effect of Glucose Load on Maternal-Fetal Transport of Cu, Se and Zn in Perfused Human Placenta: In Vitro Study

\* Nandakumar N, Al-Saleh E, Al-Shammari M, Sadan T, Al-Harni J. Obstetrics and Gynecology Department, Faculty of Medicine, University of Kuwait

#### Introduction:

Previous research from our laboratory had shown alterations in maternal-fetal status of some essential trace elements in diabetic pregnancies. Transport behavior of Cu, Se and Zn was studied in diabetic model placental perfusions, with varying glucose loads, to evaluate role of hyperglycemia per se on their transfer.

#### Methods:

Human placenta from normal pregnancies were collected post-partum. Cu, Se and Zn at twice physiologic concentrations along with antipyrine (conc. 100 mg/L) as reference marker were then injected as a single bolus (100ul) into the maternal arterial circulation of perfused placental lobules and perfusate samples collected from maternal and fetal circulations over a period of 5 minutes. National Culture and Tissue Collection medium, diluted with Earle's buffered salt solution was used as the perfusate. Experiments were done in 3 separate series with increasing glucose loads of 1g/L, 2g/L and 5 g/L in maternal perfusate to simulate diabetic state. Concentration of trace elements in perfusate samples was assessed using

atomic absorption spectrophotometry while antipyrine concentration was assessed colorimetrically.

#### Results:

Differential transport rates of Cu, Se, Zn and antipyrine in 8 perfusions did not differ significantly (Student's t-test-  $p > 0.05$ ) in euglycemic and hyperglycemic perfusions. TR50 indices of Cu, Zn and Se compared to antipyrine averaged 0.96, 0.95 and 0.96 in euglycemic series while in 2gm glucose perfusion series, the indices averaged 1.01, 0.97 and 1.03 respectively. In perfusions with 5 gm/L glucose load, the corresponding TR50 indices averaged 1.00, 1.01 and 0.99 respectively. Transport fraction indices and various pharmacokinetic indices of the 3 trace elements compared to antipyrine showed variable differences. Absorption rate- elimination rate indices of Se and Zn differed significantly in hyperglycemic perfusions.

#### Conclusions:

We report for the first time that transport behaviour of essential trace elements could be altered by hyperglycemic states with potential noxious effects on fetuses or infants of diabetic mothers. Funding Agency: Kuwait University Research Grant MO01/00

### Effect of alkylmaltoides and cyclodextrin absorption enhancers on pulmonary absorption of insulin

Hussain A1, Yang T1,\*Zaghloul A2, Ahsan F1 1School of Pharmacy, Texas Tech University HSC, Amarillo, TX 79106, USA; 2Faculty of Pharmacy, Kuwait University, POBox 24923, SAFAT 13110, Kuwait

#### Introduction:

Because of the large surface area and thin layer of alveolar epithelium, pulmonary route gained attention as an attractive alternative to parenteral route for the delivery of therapeutic peptides and proteins. Unfortunately, the absorption is limited because of the high molecular weight of these drugs. However, various absorption enhancers have been tried to increase the absorption through lungs. In the present study, we aimed at comparing the effects of tetradecyl maltoside (TDM) and modified cyclodextrin, dimethyl-beta-cyclodextrin (DMCD), on the pulmonary absorption of insulin following intratracheal administration in rats.

#### Methods:

Stock solutions of 5% (w/v) of TDM and DMCD were prepared in normal saline. Intratracheal formulations were prepared by mixing Novolin® with appropriate concentrations of the enhancers to achieve a final mixture which contained 0.25%, 0.5% or 1% of TDM or DMCD. Male Sprague-Dawley rats were used. Forty five to fifty minutes after initial anesthetization, aliquot (100 µl) of insulin (1.25 U/kg) formulation containing appropriate concentration of the enhancer was sprayed into the lower regions of the trachea using a MicroSprayer™. The trachea was visualized using a small animal laryngoscope. Blood glucose levels were measured in blood collected from the tip of the rat tail using a glucometer and plasma insulin levels were measured by a human insulin specific RIA kit.

#### Results:

There was a proportional increase in the extent of insulin bioavailability with the increase in the concentration of TDM and DMCD (0.25% through 1%). The increase in intrapulmonary absorption produced by TDM was twice as much as that produced by DMCD. DMCD showed a delayed absorption of insulin (delayed T<sub>max</sub>) compared to TDM which showed a rapid absorption (T<sub>max</sub> = 5 min). The extent of insulin bioavailability with TDM was 1.5-2 times higher than that observed with DMCD

#### Conclusions:

TDM absorption enhancer showed increased absorption of insulin delivered intratracheally compared to DMCD.

**DKA profile, The Amiri experience, 2001-2005**

1 Altora W, 1 Alattar AT, 2 Ben-Nakhi A, 2 Al-Arouj M, 2 Ahmad J  
1 Department of Internal Medicine, Diabetes Unit, Amiri Hospital

**Introduction:**

To study the profile of Diabetic Ketoacidosis (DKA) admissions and factors related to this condition.

**Methods:**

Retrospective, file based study of 283 DKA admissions for 141 patients (T1DM and T2DM) in Al Amiri Hospital – internal medical department between January 2001 and January 2005. We studied the biophysical data; and also looked into the biochemical tests which are routinely being done in case of DKA (blood PH, plasma glucose level, bicarbonate level, renal function and serum electrolytes).

**Results:**

We found that the mean age at admission was 22.8±12.7 years; the duration of hospitalization was 3.8±3.7 days and the mean blood PH at admission was 7.2±0.1. Female admissions were slightly higher (52.6%) than males, the majority (87.8%) were T1DM and 43.1% of the admissions occurred within the first 5 years since diagnosis. The classical symptoms of polyuria, polydipsia, and polyphagia as a presenting symptoms occurred only in 38.2%. Death occurred in one occasion (0.4%) and the need for ICU admission was in 2.1% of the cases, and less than 3% needed to be infused with bicarbonate. In 53.4% of the cases the precipitating factor was discontinuation of the insulin, and in 28.6% the cause was not clear.

**Conclusions:**

We conclude that despite the similarity of our DKA admissions profile with other observational studies in general, there are some dissimilarity in a number of aspects which need further investigation particularly in relation to mortality and pattern of presenting symptoms.

**Early Glomerular Changes in Diabetic Growth Hormone-Deficient Rats**

\*Malati S 1, Barac-Nieto M 1, and Francis I 2·1 Department of Physiology, Faculty of Medicine, Kuwait University; 2 Department of Pathology, Faculty of Medicine, Kuwait University.

**Introduction:**

We studied whether growth hormone (GH) plays a role in development of renal glomerular hypertrophy and hyperfiltration in diabetes using GH-deficient (dwarf) rats. The reversibility of these changes on treatments with insulin or phlorizin (PLZ), a blocker of renal sodium-glucose reabsorption, was examined.

**Methods:**

Streptozotocin diabetes was induced in male dwarf rats. Morphometry was performed on kidney sections stained with PAS, or with cytoplasmic anti-ezrin or nuclear anti-Wilm's tumor-1 podocyte antibodies. Clearances of para-aminohippurate C[sub]PAH[endsub], inulin C[sub]inulin[endsub], and renal blood flow were measured.

**Results:**

At one-week diabetes glomerular tuft area (9.5%) and ezrin positive area (54%) significantly increased and PAS-positive mesangial matrix area (MMA) did not change. Podocyte density decreased with tuft growth and unchanged podocyte number. Clearances of inulin and PAH (ml min<sup>-1</sup> 100g<sup>-1</sup>) in diabetic rats were higher than in controls: 0.82±0.07 vs. 0.47±0.02 (p<0.01) and 2.41±0.43 vs. 1.34±0.27 (p<0.05), respectively. Treatment with insulin or PLZ prevented these hemodynamic changes, but not glomerular hypertrophy nor reduced podocyte density. Treatment with PLZ, but not with insulin, prevented the increase in ezrin positive area. Diabetes caused a 3 fold increase in protein excretion rate, which was prevented by both treatments. Proteinuria correlated with glycemia r<sup>2</sup>=0.76, and Cinulin r<sup>2</sup>=0.6.

**Conclusions:**

Early diabetic glomerular hypertrophy and hyper filtration occur in GH-deficient animals. Podocyte hypertrophy was prevented by short-term normalization of the glycemia with PLZ but not with insulin, with which glycemia was more variable. Hyperglycemia is the major determinant of renal hemodynamic changes and of proteinuria of early

diabetes, since they were prevented by normalization of glycemia, despite persistent hypoinsulinemia.

Funding Agency: College of Graduate Studies

**Garlic (Allium sativum) and ginger (Zingiber Officinale) attenuate nephropathy progression in a streptozotocin-induced diabetic rat.**

Al-Qattan K\*, Thomson M, Al-Hajeri D, Al-Amin Z & Ali M. Kuwait University

**Introduction:**

A chronically diabetic kidney exhibit dire structural and histochemical modulations that are largely responsible for the deterioration and loss of clearance function, which is symptomatic of the condition. Such nephropathy is the result of the destructive effects of a multitude of biochemical abnormalities including hyperglycemia. The consensus is that euglycemia is central to controlling diabetic nephropathy. This study investigated the nephrotoxic effects of garlic and ginger on the nephropathological occurrences in streptozotocin (STZ)-induced diabetic rats.

**Methods:**

Raw aqueous extracts of garlic and ginger were administered daily (i.p. 500 mg/Kg) for a period of seven weeks into two groups (2<sub>n</sub> = 10) of diabetic rats (serum glucose > 350 mg/dl one week post-STZ injection). At the end of the seventh week the serum glucose and 24 h urine protein clearance were determined and the left kidney was processed for standard light microscopy examination and renal corpuscular space (RCS) width estimation for a control group (n = 10) and 3 diabetic groups (3<sub>n</sub> = 10) of rats.

**Results:**

Compared to the digital images (DI) of the normal kidney, the DI of diabetic kidney showed RCS shrinkage (47%, P<0.5), signs of increased glomerular density & hypertrophy, glomerular and microvascular hyalinization, enhanced protein shedding in RCS, proximal tubules (PT) basement membrane thickening, and PT cytoplasm fragmentation (Oncocytoma). In response to the herbal treatments serum glucose was less by 43-45%, (P<0.5) and the nephropathological changes, although evident, were less prominent. The good definition of the glomerulus and RCS in treated kidneys, might suggest healthier intraglomerular blood flow and glomerular filtration. This view is supported by the reduction in proteinuria (53%, P<0.5) in diabetic treated rats.

**Conclusions:**

Signs of nephropathy are evident even in the early stages of diabetes. Regular garlic and ginger intake might delay the progression of diabetic nephropathy.

**Nutritional Supplement and Hypocaloric Diet for Weight Loss: a randomized, double-Blind Trial**

\*Lyoussi B1, Ragala MA1, Chraibi A2, Mantovani S3  
1UFR Physiology-Pharmacology, University of Fez, Morocco; 2 Faculty of Medicine, Rabat, Morocco; 3 Biotherapy medical, Pegaso, Italy

**Introduction:**

Leptin is a hormone that appears as a regulator of energy balance. It is important to know whether leptin concentrations are changed under conditions of altered energy homeostasis. Studies reveal that plasma leptin levels in females are higher than those in males, and that leptin in hypertensive subjects are higher than those in BMI- matched normotensive subjects.

**Methods:**

We examined the relationships between circulating leptin concentrations in healthy subjects and Type II diabetic patients with or without hypertension as function of body mass index. Our study investigates the possible relationships between BMI , serum leptin concentration, insulin, C-peptide and IGF1 in 100 normal-weight and 100 diabetic subjects with or without hypertension. In our study we examined 100 patients of the Hospital of the region of Fez Boulemane.

**Results:**

A very close correlation between the amount of body mass index and the leptine serum concentration was found. The values of leptinemia in men of normal constitution ranged within 1-7 ng/ml, non-obese women had 3-4 times higher values. Leptinemia in some obese individuals reached up to 60 ng/ml. In the other

hand, Dietetic supplement with essential amino acids is recommended in slimming diets to its following properties: it activate the metabolism, preserves the muscular mass from depletion, it prevents putting on weight (yo-yo effect). The clinical study under placebo control has examined the effectiveness and tolerance of 3-week treatment with Aminoform 1000R, the food integrator based on essential amino acids for stimulating weight loss in a group of 20 obese people. The 20 patients took part in an aerobics programme during the study. Some parameters were evaluated for the analysis: the azotaemic profile, the glycemic and lipidic profiles, the hemo-chemical values of IGF1, C-peptide insulinemia and Leptinemia. In these subjects, the mean (±SEM) body weight reduction (3,7±0.15 kg) and body mass index reduction of (3±1.1 kg/m<sup>2</sup>). A decrease in the ratio Insulin/Glycemia is observed. Serum total cholesterol level and triglycerides decreased. Serum leptin was significantly decreased (-50%) and highly correlated to body mass index (r= 0.8). There were no changes in serum insulin and plasma IGF1.

**Conclusions:**

The study shows the effects of Aminoform 1000® and the effectiveness and tolerance are confirmed as regards placebo. These data indicate that short-term weight loss resulting from reducing percentage energy from fat, increasing physical activity and aminoacids supplements has a favorable effect on regional body composition and total and LDL cholesterol with minimal effects on HDL cholesterol, and insulin. Supplementation with Aminoform 1000R may be an important component of a weight loss program to prevent increases in cardiovascular diseases.

**Education and Self Dose Adjustment of Insulin in Pregnant Women Using an out-Patient Method in Iran**

Rajab A, Nikousokhan AK, Rajab M, Shakeri N Iranian Diabetes Society

**Introduction:**

Many studies have shown that insufficient control of diabetes during pregnancy can cause many maternal and fetal complications such as premature delivery, abortion and fetal disorders. In this article the efficacy of using education and self-dose adjustment of insulin in an out-patient method in the glucose control of diabetic pregnant women has been studied.

**Methods:**

121 pregnant diabetes (79 multipara and 42 primipara) with the average age of 29 years (SD= 5.73), average weight of 66Kg (SD= 11.7) and average history of diabetes 5 years (SD=5.06) were studied in the Iranian Diabetes Society (IDS). 50 cases had type1 diabetes, 25 cases had type2 diabetes and 46 cases had GDM. Before pregnancy 23 cases were treated with OHA, 67 cases with Insulin and 31 cases didn't receive any treatment or they were on diet. All of them participated in our 15-hour training course. They were given multiple injections and self-dose adjustment of insulin on the basis of daily control of blood glucose. They controlled their blood glucose 3-6 time/day, urine glucose and ketones 3 times/day and their weight weekly. We visited them every 4 weeks and adjusted their insulin dosage. We measured their blood HbA1c every 8 weeks and referred them to a gynecologist every 4 weeks and to an ophthalmologist every 8 weeks. Besides, they were in contact with us by the phone round the clock.

**Results:**

Before education and our treatment planning, 41.78% of multipara diabetics had history of 1-4 abortions, premature delivery, macrosomia, dead child and death of child. After our treatment planning 98.35% of diabetics had normal delivery with healthy children. The average of HbA1c at the end of pregnancy subsided from 7.18% to 5.97% with decrease of 1.21% (N.R. = 4.2-6.3%) (P=0.00).

**Conclusions:**

In the managing of pregnant diabetics, multiple injections of insulin along with education prevent maternal and fetal complications. Therefore an out-patient method for managing pregnant diabetics is completely feasible in Iran like other countries.