Abstracts

10th Annual Workshop on Diabetes Mellitus and its Complications Al Ain, United Arab Emirates

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Macrovascular disease and type 2 diabetes; are we achieving the treatment targets?

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Macrovascular disease (MVD) is the major cause of morbidity and mortality in type 2 diabetes (T2D). Its prevalence is 2-3 x higher than in non-diabetics. Many studies provide mounting evidence that tight control of hyperglycaemia, hypertension and hyperlipidaemia reduces MVD morbidity and mortality. Hence, the UK National Service Framework (NSF) stresses the importance of achieving better treatment targets for T2D. We have previously shown that patients with T2D attending various diabetes centers in UK are not achieving the recommended treatment targets for MVD. Indeed, these data confirm the belief that MVD risk factors are widely prevalent among this group of patients.

To assess the current percentage (year 2002) of patients achieving these treatment targets for MVD risk factors in our diabetes clinic, we audited 100 patients with T2D (54% on insulin) with mean age of 65 years. The data show that majority of the patiens are not achieving the targets for glycaemic and blood pressure control despite the fact that 80% are on treatment for hypertension. However, the lipids targets were achieved in 70%. MVD was diagnosed in 45% of patients.

This confirms that to achieve a tighter control, as recommended by the National Service Framework, for the majority of patients will lead to a polypharmacy policy. Many studies have shown that this is cost effective and that patient wellbeing is improved even with such policy. Innovative measures to prevent MVD as well as for treating the highest risk group are needed. Indeed, more resources are required if the benefits of the recommended treatment targets are to be widely implemented.

Perioperative morbidity in diabetics undergoing cabg - a retrospective study

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Diabetes is a recognized risk factor in patients undergoing surgery for coronary artery revascularisation (CABG). Cardiovascular diseases are the major causes of mortality in persons with diabetes (Sowers RJ, Epstein M, Frohlich ED, Hypertension 2001 37: 1053-9). We undertook a pilot retrospective study of 75 consecutive patients undergoing CABG at our institution. 54.6% were diabetics in this group, and 26.8% of them were of high risk by Euroscore compared to 5.9% of non-diabetics. Diabetics had increased perioperative morbidity. The results, the possible implications of tight glycaemic control on morbidity in patients undergoing CABG, and the need for prospective studies will be discussed.

The insulin resistance syndrome

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The Insulin Resistance Syndrome (IRS) describes a condition that is characterized by decreased tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion. This metabolic dysfunction leads to a cluster of abnormalities with serious clinical consequences, most importantly, cardiovascular disease and/or type 2 diabetes.

Individuals at risk of IRS can be identified by history, physical examination and laboratory evaluation. The characteristic abnormalities of IRS are abdominal obesity, high blood pressure, impaired fasting or postprandial glucose, high triglycerides and low HDL cholesterol. The diagnosis of IRS can be made if three or more of these characteristics are present. Other risk factors include family history of type 2 diabetes, hypertension or CVD, polycystic ovary syndrome, sedentary lifestyle, age and ethnicity.

Lifestyle modification aiming at reducing weight and increasing physical activity is appropriate for all patients with IRS. Further research into pharmacologic interventions for the treatment of IRS appears very promising.

Obesity assessment: relevance of body distribution and ethnic variations

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WHO defines obesity as a condition in which body fat content is increased to the extent that health and well being are adversely affected . The BMI cutoffs recommended for Obesity diagnosis (> 30 Kg/m^2) is based on the

assumption that at this level the total body fat is > 20% in males and >35% in females. There is growing evidence to suggest that the insulin resistance and the ensuing metabolic complications of obesity are more linked to visceral obesity than to excess subcutaneous fat content . The adverse cardiovascular outcome of isolated visceral obesity is evident in the 12 yr prospective Honolulu Heart study. Waist circumference (WC) is a good clinical surrogate to assess visceral fat content and it is well correlated with BMI, Visceral fat volume (CT estimation) and insulin sensitivity in several studies. The decrease in visceral fat with diet ,exercise and pharmacotherapy will have meaningful beneficial effects on the metabolic abnormalities. Several studies have shown different relationships between BMI and % body fat among different ethnic groups. Asians are shown to have higher body fat content at a lower BMI, compared to Caucasians. Considering the major public health implications of this observation among Asian population (more than half of world population), several organizations have recommended lower ethnic specific BMI and WC cut off points for diagnosis of obesity among Asians.

Type 2 diabetes is only the tip of the iceberg…

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Diabetes mellitus type 2 represents the final events of chronic and progressive syndrome representing a heterogeneous disorder caused by variable combinations of : Insulin Resistance and decreased B-cell function of the pancreas caused by both genetic (genetic polymorphism, islet cell defect, abdominal fat, appetite, energy expenditure…) and acquired abnormalities (diet, obesity, physical inactivity, toxins, glucose toxicity..). Currently this disease is diagnosed when the underlying metabolic abnormalities comprising of insulin resistance and decreased B-cell function leads to elevation of fasting plasma glucose above 126 mg/dl and above 200 mg/dl after 75 g glucose load (as our diagnostic indicator). However, the fact that many newly diagnosed diabetic individuals in our current practice already have the so called late complications of diabetes (both micro vascular and macro vascular) at the time of diagnosis, indicates the diagnosis may have been delayed and this detrimental metabolic abnormality is present for many years before hyperglycaemia ensues, besides that the prediabetic stage has deleterious effect on human health and mandates increased awareness by health professionals and the general public. Persons in stage I have normal glucose tolerance; attributed to ability of the B-cell of the pancreas to compensate for the Insulin resistance, at this stage dyslipidaemia (high triglycerides, variable elevation of LDL and low HDL) as well as abdominal adiposity (increased waist to hip ratio) may indicate insulin resistance that mandates medical intervention. In stage II; impaired glucose tolerance due to defect in secretory capacity of B-cells. To avoid progression to clinically overt type 2 diabetes; stage III, the ongoing metabolic disturbances (insulin resistance and metabolic syndrome) with their deleterious effects on the vascular system, various tissues and organs should be known to health professionals and consequently strategic efforts are required to avoid a world-wide growing health problem that affects more than 150 m people at the beginning of the new millennium and this number may double in the next 25 years. Type 2 diabetes is characterized by B-cell dysfunction and insulin resistance in all major target tissues; skeletal muscle, liver, kidney and adipose tissues, and both elements are well accepted as pathogenic factors. There is still controversy whether these defects have a primary genetic origin or secondary to other factors. Insulin resistance is frequently used with impaired insulin-stimulated glucose disposal in tissues responsible for insulin- mediated glucose uptake like; skeletal muscles and to a lesser degree adipose tissues. Besides lipolysis in adipose tissues and suppression of glucose production in the liver which are regulated by insulin, and there is an ongoing discussion on which target tissues is mainly affected by insulin resistance and the contribution of the various target tissues to insulin resistance. Understanding the pathophysiology and pathogenesis of insulin resistance syndrome will shed light on future treatment of type 2 diabetes.

Diabetes and pregnancy

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Early in normal pregnancy the maternal hormonal milieu lead to pancreatic β-cell hyperplasia and increase insulin release, resulting in increased peripheral G utilization, glycogen storage and decrease in hepatic glucose output, resulting in lower fasting plasma glucose. Increased erythropoeisis in pregnancy giving younger RBC's, which are less glycated, result in lower AlC.

As pregnancy progresses the diabetogenic hormones also increase some potent hormones increase between 26-32 weeks. Thus insulin sensitivity decreases by 50-70%. The glucose tolerance deteriorates in all pregnant women. The impairment is large enough to fulfill the diagnosis of GDM in 2% in US, and12% in Asia and Middle East.

Elevated glucose in the first 6 months of pregnancy leads to congenital malformation of the CNS, renal and CVS systems. To minimize these devastating malformations standards of care for all women with diabetes, who have child bearing potential, should be given and pregnancy should be avoided till euglycemia is achieved.

Risk assessment of GDM should be undertaken at the first prenatal visit in high-risk women. Both maternal and perinatal morbidity and mortality are increased in women with GDM. There are immediate and long-term morbidity risks.

Women with GDM have markedly increased risk of

developing T1DM and T2DM. Postpartum follow up is crucial, lifestyle modification should be reinforced. Several clinical trials have shown that lifestyle changes can prevent diabetes in high-risk groups.

Offspring of women with GDM/DM are at increased risk for obesity, glucose intolerance and DM in late adolescence and young adulthood.

Limitations of the oral glucose tolerance test for gestational diabetes diagnosis.

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This study was undertaken to highlight the problems of the OGTT for the diagnosis of gestational diabetes (GDM). During a 5 year period (May 1997-April 2002), 5142 patients underwent the 3-h, 100-gm OGTT at the Al Ain hospital, of which 503 (9.8%) could not be completed due to problems associated with the test. The mean maternal age was 28 years, while the mean gestational age at OGTT was 26 weeks. The major ethnic distribution of the study population was Arabs (60%) and nationals of the Indian subcontinent (23.7%). Outcome data available only on the 330 women showed 30(9.1%) neonates were over 4000 grams. 252(76.4%) deliveries were normal, 71 (21.5%) by caesarian section and 7(2.1%) resulted in abortions/stillbirths. The use of OGTT for GDM diagnosis results in the inability to establish a diagnosis in approximately 10% pregnant women. Vomiting remains a major drawback. Alternative patient-friendly "gold-standard" recommendations by expert panels are needed.

Assessing expatriate diabetic patients' self management habits

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Purpose: The purpose of this study is to explore expatriate Diabetic patients' self-management habits as the statistics shows that since the elimination of medicine supply for expatriates in the Primary health care clinics, the attendance is reduced to 8% in 2002 compared to 2000. **Methods**: 42 expatriate diabetic patients were enrolled in this study and interviewed with a questionnaire. The study focused on areas of access of care, status of control, medication, investigation and annual check. The data revealed significant gaps in all areas of management. Symptom less is considered as satisfactory management regardless of the status of control. The majority (82%) of the patients had neither visited a clinic or a hospital for one year and they were using old prescription. 73% of patients were getting their medication from their own country. **Conclusion:** The result of this study demonstrates that this particular group of patients' care perception and management need special attention. Otherwise they will end up with complications and admission to hospital which will be a huge burden not only to patients and their families but for the government as well.

The biological impact of proinsulin-c-peptide (or: do we negotiate a therapeutical option in type 1 diabetes?

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The proinsulin C-peptide fulfills an important function in the biosynthesis of insulin. However, C-peptide has generally been considered to be biologically inert. Recent studies indicate that C-peptide administration to type 1 diabetes patients is accompanied by improved renal function, amelioration of autonomic dysfunction and augmented skin and muscle blood flow. The responsible cellular mechanisms may be related to C-peptide's capacity to stimulate both Na^+K^+ATPase and eNOS. These studies raised the question that it may be reasonable to add C-peptide to the conventional insulin treatment of type 1 diabetes if metabolic control is normo-or near normoglycaemic.

Effect of duration of type 2 diabetes and endogenous insulin secretion

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OGTT was performed with measurements of plasma glucose, free insulin, and C-peptide every 30 minutes for 3 hours on 289 type 2 diabetic patients. Patients were divided according to duration of DM to Group A (≤ 1yr), B (1-5 yrs) C (>5-10 yrs), D(>10-15 yrs), and E (>15 yrs).

Basal glucose stimulated, and area under the curve for insulin (AUCI) and C-peptide (AUCC-P) showed gradual decline with advancing duration of diabetes. The AUCC-P was significantly higher in group A as compared to group B, P= 0.023, and group C, D, and E P<0.01. The AUCC-P was significantly higher in group B, as compared with group C, D, and E (p<0.01). There were no differences in the AUCC-P among groups C, D and E. The AUCI was significantly higher in group A when compared with group C, D, and E (P<0.01). There were no differences in the AUCI among groups C, D, and E.Conclusion: This study shows that endogenous insulin secretion decreases with prolonged duration of type 2 diabetes.

The role of inflammatory cytokines in experimental diabetic nephropathy

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Background: Light and electron microscopic studies of long-term diabetic rat kidney revealed a significant loss of tissue. This study examines the role of inflammation in the process of tissue loss. **Methods**: The level of cellular infiltration into the renal parenchyma of 8-month diabetic rats was examined by light and electron microscopy. Immunohistochemistry and/or Western blot analysis was used to demonstrate expression of T cell markers, macrophages and cytokines secreted by these cells. Expression of inducible nitric oxide synthase (iNOS) was also studied. **Results**: Eight month old diabetic kidneys were infiltrated by CD4+ and CD8+ cells. Moreover, a significant presence of ED1, MHC classes and I and II was observed. Although increased expression of all cytokines and T-cell markers occurred in 1 month diabetic kidneys, only CD8, MHC class I and ED1 showed significance. iNOS was not discernable at 1 month. **Conclusions**: Evidence of renal tissue damage in diabetic nephropathy is apparent within one month of disease induction. This seems to involve the activation of MHC classes I and II on macrophages and other cells followed by a cascade of events that includes the infiltration of kidneys by CD8+, CD4+ cells and the production of their cytokines. Both CD8+ and CD4+ cells might therefore be important for the progression and severity of the disease. Over expression of iNOS only at eight months suggests that nitric oxide might not be implicated in initiation of the pathology underlying loss of renal tissue. It is speculated that these renal cells probably die by apoptosis.

Craniofacial malformations and intrauterine growth retardation in a mouse model of maternal diabetes.

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Maternal diabetes is reported to cause a 2-3-fold increase in the incidence of congenital malformations in the offspring. Although fetal macrosomia is often reported in these pregnancies, poor metabolic control particularly in long-standing diabetes might lead to uterine vascular complications reduced vascular perfusion and consequently fetal growth retardation (Neiger R 1992 Clin Obstet Gynecol 35:138-150). Experimental diabetes models provide a valuable opportunity to study the fetal complications while avoiding extraneous variables inherent in clinical studies. Groups of mice were made diabetic on gestation day (GD) 2 by a single IP injection of streptozotocin freshly prepared in citrate buffer. A blood sugar level of 200 mg/dl or more determined 24 hrs later was considered to indicate diabetes. The controls were non-treated or given a proportionate volume of buffer alone. Fetuses were collected on GD 18. Unlike the control group mice, a large number of plug positive diabetic animals were found to contain no embryos/placentas possibly as a result of implantation failure. There was a consistent incidence of intrauterine growth retardation in the diabetic group. Growth retarded fetuses were also often severely malformed. Several craniofacial anomalies including maxillary-mandibular hypoplasia, arched palate, microstomia, astomia and occasional facial clefts were also observed. About 50% of fetuses had holoprosencephaly associated with a proboscis, median eye, astomia, micoglossia, and mandibular and maxillary agnathia. There were considerable inter-individual and inter-litter variations in the severity and combinations of these anomalies. Alizarin red-S and alcian blue stained skeletal preparations revealed the hypoplasia of various facial bones and basicrainal bones. Those with obvious neural tube defects had severe malformations of the basicranial bones. The spectrum of craniofacial anomalies observed here suggests that the neural crest cells are particularly susceptible to maternal diabetes in this mouse model.

(This work was generously supported by the UAE University)

Effects of volatile anaesthetics on contraction in ventricular myocytes from streptozotocin-induced diabetic rat

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In addition to producing unconsciousness several widely used volatile general anaesthetics including halothane, sevoflurane, desflurane and isoflurane also have various inotropic effects on the heart (1). We have investigated the effects of these volatile anaesthetics on contraction in ventricular myocytes from streptozotocin (STZ) - induced diabetic rats. Electrically stimulated (1 Hz) myocytes, maintained at 30-31 ºC, were superfused with either normal Tyrode (NT) solution or NT containing anaesthetic (1 mmol/l) for a period of 2 minutes. Characteristics of myocyte contraction including time-course and amplitude of shortening were measured with a video edge detection system. Exposure of control myocytes to halothane produced a transient positive, followed by a sustained negative inotropic effect. Exposure of myocytes to sevoflurane, on the other hand, generally produced a sustained negative inotropic followed by a transient positive inotropic effect during wash-off with NT. Isoflurane and desflurane generally produced sustained negative inotropic effects. Prolonged time-course and altered amplitude of shortening has been frequently reported in STZ-induced diabetic rat heart (2,3). The effects of anaesthetics on contraction in myocytes from control and STZ-induced diabetic rats were investigated.

1. Davies LA *et al*, (1999), Brit J Anaes, 82(5): 723-730
2. Howarth FC *et al*, (2002), Pflugers Arch, 444:446-451
3. Choi KM *et al*, (2002), Am J Physiol, 283:H1398-H1408

Does intensive insulin therapy have a role in the acute care setting?

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Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had

diabetes. There is recent evidence that the use of intensive insulin therapy improves outcome in patients admitted to the surgical intensive care unit. A recent 12 months prospective, randomized controlled study involving 1548 patients showed that intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6% ($P<0.04$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusion by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive insulin therapy were less likely to require prolonged mechanical ventilation and intensive care. In addition, The Diabetes and Insulin Therapy in Acute Myocardial Infarction (DIGAMI) study has clearly shown that intensive insulin therapy improves long term survival in diabetic patients with acute myocardial infarction and the effect seen at one year continues for at least 3.5 years, with an absolute reduction in mortality by 11 percent.

Although strict control of glycemia is suggested to be the principal factor, the improved outcomes observed in the groups receiving intensive insulin therapy may have resulted from the inhibitory actions of insulin on cytokines released during acute illness such as tumor necrosis factor TNF-alpha and Macrophage inhibitory factor (MIF).
Conclusion: Intensive insulin therapy reduces morbidity and mortality among patients in acute care settings.

Comparison of combination of sulfonylureas with nph insulin at bed time or regular insulin before meals in type 2 diabetic patients failing sulfonylurea therapy

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In a randomized prospective, crossover study, 18 patients with type 2 DM failing Glipizide (GP) therapy were studied. Patients were randomized to receive either combination of GP and NPH insulin at bed time or GP and Regular insulin before meals for 12 weeks then crossed over to alternate therapy for another 12 weeks. Fasting glucose, Insulin, C-peptide, Hb Alc, and lipid profiles were serially determined. OGTT and ITT were done with measurements of arteriovenous differences in blood glucose an forearm glucose uptake.

Hb Alc decreased from baseline of 9.1% to 8.1% in the NPH group and 7.2% in regular group ($p= 0.003$). Fasting glucose was similar between the two groups and fasting insulin level was significantly higher in the NPH group. Fasting and glucose stimulated C-peptide levels were significantly higher in the regular group. Forearm glucose uptake was not different between groups. Total daily insulin dose was higher in the regular group; however it did not correlate with HbAlc. Lipid profiles improved in both groups.

The time course of changes in amine concentrations in the rat tail artery following induction of diabetes with streptozotocin.

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The effects of STZ-diabetes on amine metabolism had been studied in the tail artery of the rat. Several weeks after the induction of diabetes the concentrations of noradrenaline, dopamine and serotonin increase markedly. The artery is long (15-20 cms) and changes are similar in proximal, middle and distal sections of the artery. The peak of amine concentrations is consistently between 10 and 20 weeks but the levels remain raised, particularly in the distal portion of the artery, throughout the period of the study (up to 42 weeks after STZ injection).

Effects of halothane on intracellular ca^{2+} in ventricular myocytes from streptozotocin-induced diabetic rat

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A variety of alterations in contraction including prolonged timecourse and altered amplitude of shortening have been reported in ventricular myocytes from streptozotocin (STZ)-induced diabetic rat (1,2). Altered mechanisms of Ca^{2+} transport may underlie these contractile dysfunctions (1,2). Volatile general anaesthetics, including halothane, in addition to producing unconsciousness, also have a potent negative inotropic effects on the heart (3). We have investigated the effects of halothane on contraction and Ca^{2+} transport in ventricular myocytes from STZ-induced diabetic rat. Experiments were performed in electrically stimulate (1 Hz) myocytes superfused with a normal Tyrode solution maintained at 35-36 ºC. Shortening was measured with a video edge detection system. Intracellular Ca^{2+} concentration was measured in fura-2 AM loaded myocytes with a fluorescence photometry system. Timecourse of contraction and Ca^{2+} transient were prolonged and amplitude of Ca^{2+} transient was reduced in STZ compared to control myocytes. Halothane reduced amplitude of contraction and Ca^{2+} transient, decreased sarcoplasmic reticulum Ca^{2+} content and myofilament sensitivity to Ca^{2+} to similar extents in STZ and control myocytes. In conclusion the effects of halothane on myocyte contraction and Ca^{2+} transport were not altered by STZ-treatment.

1. Howarth FC *et al*, (2002), Pflugers Arch, 444:446-451
2. Choi KM *et al*, (2002), Am J Physiol, 283:H1398-H1408

3. Davies LA *et al*, (1999), Brit J Anaes, 82(5):723-730

Cushing's syndrome caused by unsupervised use of ocular glucocorticoids

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Objective: To report a case of Cushing's syndrome caused by prolonged and unsupervised use of glucocorticoid ocular drops. **Method:** We present the clinical and laboratory findings and describe the clinical course of the patient **Result:** A 31 year-old man with history of extensive ophthalmologic complaints and procedures on chronic use of glucocorticoid ocular drops was referred for new onset diabetes mellitus. Clinically, the patient appeared cushingoid with buffalo hump, thin skin, bruises, and purple striae. Laboratory evaluation revealed a very low serum cortisol level with a concomitantly low-normal ACTH level. The response to ACTH stimulation test was abnormal indicating suppression of the adrenal glands. Following the discontinuation of eye drops, cushingoid features gradually faded away with normalization of blood pressure and serum glucose levels. **Conclusion:** Prolonged unsupervised use of glucocorticoid ocular drops may result in Cushing's syndrome with all its complications.