Abstracts
3rd International Symposium on Diabetes Mellitus and its Complications

Budapest, Hungary
01-06 July 2001

A1

A Clinical Trial of Chronic Care Diabetic Clinics in General Practice in the United Arab Emirates: A Preliminary Analysis.

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Control of diabetes mellitus is a high priority for primary health care systems. One innovative method of diabetes care delivery is the use of structured diabetes care in primary care. This includes the use of chronic care diabetes clinics or mini-clinics operated by general practitioners in primary care. There is limited experience with this model in non-Western settings. This study seeks to evaluate a multi-component structured approach to diabetes care in primary care including chronic care diabetes clinics in a newly developed country in the Arabian Gulf. The study design used is a controlled before-after methodology. Three primary health centers were chosen for the intervention with six of the remaining clinics in a Health District being used as controls. A multifaceted intervention was initiated in the intervention clinics composed of chronic care diabetes clinics, a diabetic flow chart, and educational programs for clinic nurses and doctors and patients. The study intervention took place over a period of 18 months with three diabetic outcomes (fasting blood glucose, blood pressure and cholesterol) and adherence to seven diabetes guidelines being compared for the year prior to the intervention and during the last 12 months of the intervention period. Knowledge and satisfaction questionnaires were also administered to intervention and control subjects at the end of the study. In this study, 219 subjects were enrolled (130 males and 89 females). They had a mean age of 51.6 years and a mean of 3.1 years of formal education. Of these 109 were enrolled in one of three clinics that had a chronic care diabetes clinic and 110 were enrolled in one of the six control clinics. Subjects had diabetes for a mean of 7.8 $\pm$ 4.8 years and the majority was treated with pharmacological therapy. Baseline characteristics in the intervention and the control clinics were similar with the exception of younger age ($p=0.01$) and a trend for more males ($p=0.06$) in the intervention clinics. There was a statistically insignificant change noted with the intervention in the three clinical outcomes studied (fasting blood glucose, blood pressure and cholesterol) both in comparison to the control group before and after and within the intervention group. However

most changes noted were in the expected direction of improvement. Six of the seven guidelines were statistically improved in the intervention group when compared with the control group. Within the intervention group, adherence with five of seven guidelines was also statistically significantly increased with the remaining guidelines showing a trend in favor of improvement (fasting blood glucose measurements (p=0.07) and urine determinations for protein (p=0.07)). Knowledge questionnaire scores were similar between the intervention and control groups on completion of the study but 2 of 4 items on a satisfaction scale were statistically significantly higher in the intervention group. The intervention described in this setting was successful in improving adherence to diabetes guidelines and increased some aspects of satisfaction with diabetes care. The intervention did not result in a statistically significant improvement in clinical outcomes but changes noted were in the expected direction of improvement. The significant improvement in adherence to diabetes guidelines suggests that this intervention is a promising model for diabetes care for newly developed countries.

A2

Pancreatic Diabetes Mellitus: Contradictions and Complications

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According to the general view, the therapy of pancreatic diabetes mellitus is contradictory. It has been claimed that long-term diabetic complications occur rarely and in a less severe form in pancreatic diabetes mellitus (PDM). The present study compared the metabolic status and long-term diabetic complications (retinopathy, neuropathy and nephropathy) of patients with Type I diabetes mellitus (Type I DM) with pancreatic diabetes mellitus (PDM). Diabetic complications were investigated with cardiovascular reflex test, neurometer, mini-Doppler, ophthalmoscopy and biochemical techniques in 80 patients with Type I DM and 80 patients with PDM. The prevalence of diabetic complications in Type I DM and PDM was 41% and 15% for background retinopathy, 8% and 5% for proliferative retinopathy, 5% and 61% for peripheral sensory neuropathy (PSN), 19% and 34% for autonomic parasympathetic neuropathy (APN) in Type I DM and PDM patients, respectively. The prevalence of retinopathies, PSN and APN was significantly different in Type I DM and PDM patients. There was no significant difference in the prevalence of autonomic sympathetic neuropathy (borderline: 16% vs. 12%, pathologic: 3% vs. 7%) and nephropathy in the two groups of patients. In conclusion, the prevalence of retinopathy is different in the two groups and more characteristic of Type I DM. Both the PSN and APN occur more frequently in PDM compared to Type I DM. The prevalence of these complications increases with the duration of diabetes. The frequency of nephropathy is similar at a later stage. More attention should be paid to early detection and optimal therapy of different complications in PDM.

A3

Abnormal Vascular Coiling of the Umbilical Cord in Gestational Diabetes Mellitus

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The study tested the hypothesis that abnormal coiling of the umbilical cord is a feature of the neonates of diabetic mothers in a prospective study of the maternities of 57 diabetic mothers and 389 mothers free of medical disorders in normal term pregnancies. The umbilical coiling index was derived by dividing the number of complete coils by the unstretched length of the cord. The frequency distribution of the coiling index was normal in both diabetic and control mothers. This distribution was used to derive four groupings of the cord according to the coiling index values: noncoiled; hypocoiled, less than 10^{th} centile (0.17); normocoiled , between the 10^{th} and 90^{th} centile (0.17-0.37) and hypercoiled, more than 90^{th} centile (greater than 0.37). Noncoiling and hypercoiling of the umbilical cord occurred with increasing frequency (respectively 10.5% and 12.3%) in diabetics compared with (2.1% and 8.1% respectively) controls. ($p<0.004$ and $p<0.008$, respectively. Both abnormalities of the umbilical cord were also significantly associated with adverse perinatal outcome ($p<0.04$) and emergency caesarean section delivery ($p<0.0001$) in the diabetic and normal control ($p<0.03$; $p<0.0001$, respectively) mothers.

It is concluded that neonates of diabetic mothers are more likely to have hyper-coiled or non-coiled umbilical blood vessels. Perinatal morbidity and emergency caesarean delivery are increased in this subgroup.

A4

Intrauterine Growth Retardation in Experimental Diabetes. Possible Role of the Placenta.

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Pregnant Wistar rats were injected (ip) with a single dose of 50 mg/kg of streptozotocin (STZ) on gestation day (GD) 2 and a blood glucose level of 200 mg/dl or more determined 24 hrs later indicated diabetes. The controls were non-treated, buffer treated or, following confirmation of diabetes, injected with a single dose of 2-6 IU of insulin (Novo Ultralente) once daily. Fetuses and placentae were collected from GD 14 - 20. Intrauterine growth retardation (IUGR) in STZ group was significant as early as GD 15 and persisted to GD 20. Insulin produced a significant recovery in fetal weight gain. The placentae of STZ-treated group were significantly heavier than those of the control groups. The reduction in cord length of the STZ group became apparent on GD 16 and remained so to term. The placenta of GD 14 STZ group had a thicker deciduas basalis and dilated maternal sinusoids. By GD 16, the decidua basalis contained scattered glycogen cells confirmed by Best carmine with or without diastase. The glycogen cells of the basal zone were more abundant, and had degenerated in some sites leaving behind cysts with eosinophilic mass. The giant cells had proliferated enormously. The labyrinthine zone appeared spongy with persistent fetal mesenchyme, perivascular fibrosis, and enhanced placental barrier. The trophoblasts of the labyrinths also contained abundant glycogen unlike the controls. By GD 18, the deciduas basalis of the STZ group was thinner than that of the controls and contained necrotic giant cells and lymphocytic aggregations. In the basal zone, the

giant cells had proliferated further; more glycogen cells had degenerated. Perivascular fibrosis was still extensive in the labyrinthine zone. Bloodless maternal sinusoids, extensive vacuolization, degeneration of glycogen islands and cysts formation characterized the labyrinthine zone. These changes varied in intensity from one area to another in the same placenta and between placentae of the same and of different litters. The development of the upper and lower jaws, elevation and fusion of palatal shelves, reduction of physiological umbilical hernia, descent of the testes, fusion of the urethral folds and separation of digits of the paws were significantly delayed in the STZ group. The consistent association of placental pathology with fetal growth retardation is suggestive of an alteration in placental function possibly contributing to IUGR in STZ-induced diabetes in rats.

A5

Characterization of Contraction in Ventricular Myocytes from Streptozotocin Treated Adult and Neonatal Rats.

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Administration of streptozotocin (STZ) to rats causes pancreatic β-cell necrosis, a reduction in the ability of these cells to produce insulin and an associated impairment of glucose transport. We have investigated the effects of administering STZ to young adults aged 6-8 weeks compared to neonatal rats aged 2-3 days (neonatal model) on the characteristics of ventricular myocyte contraction. Cells were isolated using a combination of enzymatic and mechanical dispersal techniques and contraction was measured using a video edge detection system. In the adult model at 10 months after treatment bodyweight and heart weight were reduced and plasma glucose increased in STZ treated animals compared to control. In the neonatal model these parameters were not altered however, glucose uptake was significantly impaired in STZ treated animals compared to control. In the adult model the characteristics of myocyte shortening (1 Hz) included a significant ($p<0.01$) increase in the amplitude of shortening (4.63±0.28 vs. 3.30±0.33 %) and a reduction in the time to half relaxation (54.4 ± 2.7 vs. 86.3±ms) with no significant ($p>0.05$) effect on time to peak contraction in myocytes from STZ compared to control, respectively (Howarth *et al*., 2001, Emirates Medical Journal, 19,1, 35-41). By contrast, in the neonatal model no significant differences were observed to the amplitude or kinetics of shortening. The absence of contractile defects in the neonatal model at 10 months after STZ treatment may be attributable to a partial recovery of the β-cells during the period of rapid growth in early life.

A6

Autonomic Neuropathy and Cardiovascular risk: the Eurodiab IDDM complications study.

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Autonomic neuropathy (CAN) is associated with poor prognosis. Prevalence of CAN and potential risk factors have not been definitely identified up to now. The EURODIAB IDDM Complications Study involved the examination of randomly selected Type I diabetic patients from 31 centres in 16 European countries. Data from 3007 patients were analysed. Symptoms and two tests of autonomic function were assessed. The prevalence of CAN was 36% with no sex and geographical differences. The frequency of one and two abnormal reflex tests was 30% and 60%, respectively. 30/15 ratio was abnormal in 24% of patients, while 18% had orthostatic hypotension, defined as >20 mmHg fall in blood pressure after standing up. Significant correlations were observed between the presence of abnormal 30/15 ratio and age ($p < 0.01$), diabetes duration ($p < 0.0001$), HbA1c ($p < 0.0001$), retinopathy ($p < 0.0001$) and albuminuria (0.0001). As a key finding, an abnormal 30/15 ratio was also related to cardiovascular disease ($p < 0.0001$) as well as to severe hypoglycaemia ($p < 0.05$), and ketoacidosis ($p < 0.0001$). Risk factors such a cigarette smoking ($p < 0.0001$), HDL-cholesterol ($p < 0.01$) and triglyceride ($p < 0.001$), were also related to CAN. Frequency of fainting on standing was observed in 18% of patients while 4% of patients had nocturnal diarrhoea. In conclusion, the present study identified previously known and new potential risk factors for the development of autonomic neuropathy, which may be important for the development of risk reduction strategies.

A7

Electrophysiological Changes in Diabetic Neuropathy: from Subclinical to Alterations to Disabling Abnormalities

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The clinical spectrum of diabetic neuropathy is variable; it may be asymptomatic but once established, it becomes irreversible and disabling. Some investigators suggested that the earliest change in diabetic nerve function is alteration in axonal excitability due to changes in ion conductance of axon membrane. However, it is still unclear if functional changes of ion channels necessarily cause permanent damage of the axonal membrane and degeneration of nerve fibres. Among various parameters of systemic nerve conduction studies in subclinical patients, prolonged F-wave latency in either upper or lower extremities seems the commonest abnormality. Decrease in amplitude of the compound sensory action potential of sural nerve is another early abnormality, which is accompanied by a fall in motor amplitude of peroneal and tibial nerves in advanced patients. In disabled patients no motor response is often elicited in the legs. Previous electrophysiological experiment did not make clear if central axons were involved or not in diabetic neuropathy. Recently, our own group has demonstrated that somatosensory central conduction time from the spinal cord to the primary sensory cortex is prolonged as well as peripheral conduction in diabetics, which might be partly responsible for the irreversible clinical presentation of diabetic neuropathy

A8

Neurogenic Inflammation of Gingivomucosal Tissue in Streptozotocin Diabetic Rats.

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Previously, it was assumed that nerve fibres are involved in the neurogenic inflammation induced by mechanical or chemical irritations. It has also been suggested that small, unmyelinated nerve fibres are impaired in diabetes mellitus as a result of diabetic neuropathy. Therefore our aim was to study the alterations of nerve processes in the gingivomucosal tissue in streptozotocin diabetic rats. Light and electron microscopical examinations were made to analyse the changes in the nerve fibres. After streptozotocin treatment the gingivomucosal tissue has a heavy inflammatory cell infiltration and some degenerated nerve fibres were observed, where dense mitochondria, disorganisation of cells organelles and appearance of myelin-like dense bodies were found in the axons. Morphometric analysis showed that 14 ± 4 % of the unmyelinated fibres degenerated after one week of streptozotocin treatment. Degeneration of myelinated fibres was not observed at this stage. Two weeks after streptozotocin treatment most of the myelinated and unmyelinated nerve fibres showed degeneration (86 ± 5%). The myelin sheath was disrupted and dark axoplasm with cytolysosome became manifest. These findings demonstrated that both myelinated and unmyelinated nerve fibres are altered, and increased inflammatory reactions exist in gingivomucosal tissue in the early stages of diabetes mellitus.

A9

The Effect of Long -term Diabetes on Rat Kidneys

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We undertook to assess the long-term effects of streptozotocin-induced diabetes mellitus on rat kidneys. Morphological, insulin-like growth factor receptor as well as apoptotic changes were studied. Using light and electron microscopy, morphological changes in rat kidneys diabetic for eight months and controls were evaluated. Kidney sections from both diabetic and control rats were stained with haematoxylin and eosin. Ultrathin kidney sections were examined using a transmission electron microscope. The levels of insulin-like growth factor-1 receptors were investigated using receptor autoradiography. Expression of pro-apoptotic molecules was studied using Western-blot analysis. Morphological differences between normal and diabetic kidneys were observed in both the cortex and medulla. The levels of insulin-like growth factor-1 receptors were significantly decreased in the cortex and the medulla of the diabetic rats compared to controls. Pro-apoptotic molecules like p53 were found to be elevated in rat kidneys diabetic for eight months compared to controls. Our results demonstrated extensive morphological loss of renal tissue on both light and electron microscopy. Using electron microscopy, apoptotic cells at various stages were observed throughout the kidney tissue indicating that the observed morphological loss could be due to apoptosis. A reduction of kidney insulin-like growth factor -1 receptors after long-term diabetes

mellitus could be due to the extensive tissue loss observed. It could therefore be speculated that insulin-like growth factor-1 might be beneficial in long-term diabetes mellitus to prevent the degeneration and/or regenerate damaged renal tissue.

A10

Diabetes Mellitus is associated with a decrease in Vasoactive Intestinal Polypeptide in Rat Gastroduodenal Tissue.

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Vasoactive intestinal polypeptide (VIP) is an inhibitory non-adrenergic, non-cholinergic transmitter, which mediates in relaxation of sphincters. The aim of this study was to determine whether there is a change in the pattern of innervation and tissue content of VIP in the rat gastroduodenum after the onset of streptozotocin-induced diabetes mellitus. VIP was localized and measured in normal and diabetic rat gastroduodenal tissues by immunohistochemistry and radio-immunoassay, respectively. VIP immunoreactivity was stronger in the ganglion cells of the submucosal and myenteric plexuses of the gastric antrum and duodenum of normal rats ($n = 6$) when compared to that of diabetic rats ($n = 6$). The VIP content of the gastric antrum and duodenum of diabetic rat was significantly ($p < 0.05$) lower than that of normal rat. In contrast to the lower tissue levels of VIP in the gastroduodenal segment of diabetic rats, the plasma level of VIP was significantly ($p = 0.04$) higher in diabetic rats compared to normals. A low tissue level of VIP in the gastroduodenal tract may be a cause of abnormal gut motility observed in diabetic patients.

P1

The role of leucine-enkephalin on insulin and glucagon secretion from pancreatic tissue fragments in rat.

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Leucine-enkephalin (Leu-Enk) has been shown to be present in the pancreas (Adeghate et al., Peptides, 17:503-9, 1996) and may play a role in the modulation of hormone secretion from the islet of Langerhans. Since literature data on the effect of Leu-Enk in the endocrine pancreas is meager and controversial, it was the aim of this study to determine the role of Leu-Enk on insulin and glucagon secretion from isolated pancreatic tissue fragments of rat. Pancreatic tissue fragments were incubated for 1 h with different concentrations (10^{-12} - 10^{-6} M) of Leu-Enk. The quantity of insulin and glucagon induced the Leu-Enk was determined by radioimmunoassay. Leu-Enk induced large and significant ($p < 0.05$) increases in insulin and glucagon secretion from the pancreas of normal rat when compared to basal. Leu-Enk-evoked insulin and glucagon secretion was inhibited by atropine, yohimbine and naloxon. In conclusion, Leu-Enk is a strong secretagogue of insulin and glucagon secretion and may exert its effect via alpha2-adrenergic, cholinergic and opioid receptors.

P2

Catecholamines in the Heart and Adrenal gland of the Streptozotocin-diabetic rat.

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The concentrations of noradrenaline (NA), adrenaline (ADR), 5-hydroxyindoleacetic acid (5-HIAA), serotonin (5-HT) and dopamine (DOP) were studied in the left ventricle and the left adrenal gland of control and streptozotocin (STZ)–treated rats at various intervals after the induction of diabetes using HPLC. The only amines detected in the heart were NA, 5-HIAA and DOP, whereas those detected in the adrenal gland were NA and ADR. Differential changes in the catecholamine concentrations occurred in the heart and the adrenal gland at different stages of the metabolic disorder. In the heart the initial changes in short –term diabetes included an increase in NA concentration but this did not persist in the longer-term diabetic animals (30-38 weeks following STZ injection). In the adrenal there was an initial reduction followed by a steady increase in the concentration of NA and ADR throughout the period of the study.