

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Epidemiology of Reproductive and Hormonal Factors in Thyroid Cancer: Evidence from a Case-Control Study in the Middle East

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Thyroid cancer is the second most common neoplasm among women in Kuwait and several other countries in the Middle East. Most of these countries also have relatively high birth and total fertility rates. To examine potential relationships between reproductive and hormonal factors and thyroid cancer, we conducted a population-based case-control interview study among 238 women diagnosed with thyroid cancer and a similar number of individually matched controls in Kuwait. Among the demographic variables, women with 12+ years of education had a significantly reduced risk of thyroid cancer (OR = 0.4; 95% CI: 0.2-0.8; p-trend <0.05). The average age at diagnosis (+/- SD) of thyroid cancer was 34.7 +/- 11 years. Events such as age at menarche, pregnancy, menopausal status and age at menopause were not associated with thyroid cancer. There was an association with age at last pregnancy and parity. Women who had their last pregnancy at ages > or = 30 years were at a significantly increased risk (OR = 2.1; 95% CI: 1.2-3.8); there was also a significant trend in risk with increasing age at last pregnancy. There was a modest increase in risk among women who had borne > or = 5 children (OR = 1.5; 95% CI: 0.9-2.5). A joint analysis of these factors showed that childbearing during the latter half of reproductive life had a substantial effect on the incidence of thyroid cancer; for any given level of parity, there was about a 2-fold increased risk if the age at last pregnancy was > or = 30 years. A substantial recent-birth effect, in relation to subsequent diagnosis of thyroid cancer, was observed during the second and third year after a birth (OR = 2.0; 95% CI: 1.0-4.1). In contrast, spontaneous abortion seemed to have a protective effect. There was a significant decrease in risk among women who had a miscarriage as outcome of first pregnancy (OR = 0.1; 95% CI: 0.03-0.4) and those who had experienced > or = 3 miscarriages (OR = 0.3; 95% CI: 0.1-0.8; p-trend <0.05). Overall, any female hormone use was not associated with thyroid cancer risk. New association is suggested for a history of post-partum thyroiditis (OR = 10.2; 95% CI: 2.3-44.8). These data support the hypothesis that reproductive factors and patterns may influence, or contribute to, the risk of thyroid cancer among women.

Antioxidant Enzyme Level in the Testes of Cirrhotic Rats

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Objectives: An understanding of the tissue and organ level of antioxidant enzymes that scavenge reactive oxygen species may provide an indication of their susceptibility to free radical-related cytotoxic damage. A direct association between testicular production of excessive reactive oxygen species and male infertility has been noted. We measured the activities of superoxide dismutase and glutathione peroxidase in the testes of thioacetamide-induced cirrhotic rats.

Methods: Antioxidant enzyme activities and trace element levels (copper, zinc, manganese, and selenium) in the testes of thioacetamide-induced cirrhotic and control rats were measured. The statistical difference between the experimental and control groups with regard to the activities of superoxide dismutase and glutathione peroxidase and levels of trace elements was analyzed with Student's t test.

Results: Our results showed a significant decrease in the activity of these enzymes in the testes of cirrhotic rats. The testicular levels of copper, zinc, and manganese, which are associated with these antioxidant enzymes, increased, whereas selenium decreased slightly in cirrhotic rats; that decrease was not statistically significant. **Conclusions:** Our studies showed a drastic decrease in the level of antioxidant enzymes in the testes of cirrhotic rats that could have deleterious effects on sperm function in these animals. Further studies are necessary to understand the exact pathways of trace element metabolism in the testes of cirrhotic rats.

Determinants of Glycated LDL Levels in Nondiabetic and Diabetic Hyperlipidaemic Patients in Kuwait

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Background: Glycation and oxidative modification of lipoproteins enhance the uptake of these lipids by macrophages in the early stages of atherogenesis. Measurement of blood levels of modified LDL particles could thus constitute another useful modality in identifying subjects at high risk of coronary atherosclerosis (CHD).

Objective: To measure the glycated LDL level and assess its associations with other metabolic parameters in diabetic and nondiabetic hyperlipidaemic subjects attending a Lipid Clinic in Kuwait. **Subjects and methods:** One hundred thirty-three hyperlipidaemic (HL) (72 nondiabetic (ND); 61 diabetic (D)) patients and 42 healthy control (HC) subjects had their fasting serum samples analyzed for glucose, total cholesterol (TC), triglycerides (TG), urate, HDL, LDL (by routine autoanalyzer methods), apolipoproteins A1 and B (by nephelometry), fructosamine (by spectrophotometry) and glycated LDL (gLDL) by ELISA.

Results: The serum gLDL level was significantly higher in HL[D+ND] than in HC ($p < 0.001$). Within the HL group, the DHL patients had higher levels than the NDHL [$p < 0.001$]. These differences were maintained when the gLDL level was also expressed as a percentage of the apo B concentration. The gLDL level correlated positively ($p < 0.01$) with those of glucose, TC, TG and LDL and negatively with HDL ($p < 0.05$) in all the subjects as a whole, healthy and hyperlipidaemia [HC+HL]. In the HL (D+ND) group as a whole, gLDL correlated significantly only with glucose [$p < 0.01$]. In group DHL, however, gLDL correlated significantly with glucose, fructosamine and LDL [all $p < 0.05$].

As expected, fructosamine levels were highest in the DHL group. The significant correlations established between fructosamine and the different analytes measured in the different subject groups were essentially similar to those observed for gLDL, except for the finding of persistent significant negative correlations of fructosamine with LDL in all the subject groups. **Conclusion:** (i) Serum gLDL levels are increased in hyperlipidaemic patients and are further increased with diabetes, suggesting that the significant glycation of LDL occurs in all hyperlipidaemic patients irrespective of their glycaemic status. (ii) The significant correlation of gLDL with glucose and fructosamine in diabetic patients would suggest its potential utility as another index of medium term glycaemic control. (iii) gLDL is easily measurable and its values could provide additional information in ascertaining an individual's aggregate CHD risk.

Ischemic Renal Disease in Kuwait

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Ischemic renal disease (IRD) is a frequent cause of end-stage renal disease. Its prevalence is mainly known from autopsy or retrospective arteriographic studies. This prospective study was conducted in 115 subjects selected from 732 patients with advanced chronic renal failure (CRF). Only patients with clinical features suggestive of IRD were selected for this study. In addition to detailed clinical and laboratory evaluation, captopril renal scintigraphy was performed in selected cases. All subjects underwent renal arteriography and all were followed up for 18.4 +/- 11.4 months. Renovascular disease was seen in 15 patients and significant bilateral renal artery disease leading to IRD was observed in 13 (11.3%). Hence the prevalence of IRD in the advanced CRF patients was 1.7%. The majority of patients with IRD (8 [61%]) were above 46 years of age and there were more men than women (10:3). Atherosclerotic renovascular disease was the most common (10 [77%]), even though arthritis (1 [7.6%]), and fibromuscular dysplasia (2 [15.3%]) were also observed. Serum creatinine at time of presentation was significantly higher in patients with IRD (784 +/- 292, p = 0.043) compared to those who did not have IRD (359 +/- 126). Corrective procedures were performed in 5 patients. After treatment the improvement in serum creatinine in patients with IRD at 3 and 6 months (166 +/- 32 and 173 +/- 47, respectively) was significantly different (p < or = 0.05) compared to those who were not treated (610 +/- 194 and 645 +/- 220, respectively). Hyperlipidemia, coronary artery disease and peripheral vascular disease were more prevalent in patients who had IRD compared to those with renal failure. The incidence of diabetes mellitus were similar in both groups. This study denotes a lower prevalence of IRD in the advanced CRF population; they had more severe renal failure at presentation but specific corrective treatment delayed progression of renal disease significantly.

Imported Visceral Leishmaniasis: Diagnostic Dilemmas and Comparative Analysis of Three Assays

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The present study evaluates the performances of three noninvasive serological assays for the detection of immunoglobulin G antibodies to leishmania antigen for the diagnosis of imported cases of kala azar (visceral leishmaniasis [VL]) in a country, Kuwait, where the disease is not endemic. A total of 323 individuals including 21 patients with documented cases of VL, 72 individuals with suspected cases of VL, 155 patients with other parasitic infections, and 75 healthy control individuals were tested by indirect hemagglutination assay (IHA; Behring Diagnostics GmbH, Marburg, Germany), indirect fluorescent-antibody assay (IFA; bioMerieux sa, Marcy l'Etoile, France), and a qualitative membrane-based immunoassay with recombinant leishmania antigen K39 (strip-test; Intersep Ltd, Berkshire, United Kingdom). Our data show that IHA is the most sensitive test (100%), followed by IFA (86.6%) and the strip-test (80.0%). The strip-test was the most specific (100%) of the three assays, followed by IFA (93.0%) and IHA (86.0%). However, the strip-test failed to detect at least three confirmed cases of VL. We conclude that IHA is preferred over IFA and the strip-test for the screening of individuals with suspected cases of VL, especially in a country where VL is not endemic and where the number of cases is regular but limited. The details about some of the patients with VL are presented to highlight the diversity of clinical presentations and problems encountered in the diagnosis of VL in a country where VL is not endemic.

Performance of Students in the Final Examination in Paediatrics: Importance of the "Short Cases"

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Aims: To determine which component of the final examination in paediatrics at Kuwait University best predicted the final outcome.

Methods: The performance of 356 medical students in the short cases, the long case, multiple choice questions (MCQs), and the essay components of the final examination in paediatrics at Kuwait University was correlated with the final grade, and the mean difference between each component and the final score calculated.

Results: The correlation was highest for the short cases, followed by MCQs, the long case, and essays. The mean difference between the final score and that of short cases was not significant, but was highly significant for the other components.

Conclusion: Results show that performance in the short cases component of the final examination in paediatrics is a better discriminator of competence than that in the long case.

Serum Lipoprotein(A) Concentration as a Cardiovascular Risk Factor in Kuwaiti Type 2 Diabetic Patients

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Serum lipoprotein(a) [Lp(a)], a risk factor for coronary heart disease (CHD) in some nondiabetic populations, is largely under genetic control and varies among ethnic and racial groups. We evaluated serum Lp(a) concentration and its relationship with traditional CHD risk factors (age, sex, smoking, hypertension, dyslipidemia) as well as stage of diabetic nephropathy in 345 type 2 diabetic patients. Lp(a) concentration was skewed with median (2.5th, 97.5th percentiles) of 25.0 (8.1, 75.7) mg/dl. Twenty-three of 55 (41.8%) patients with CHD had increased (>30 mg/dl) Lp(a) compared with 102 of 290 (35.1%) patients without CHD ($P=.35$). Twelve of 27 (44.4%) female patients with CHD had increased Lp(a) compared to 11 of 28 (39.3%) males ($P=.70$). Lp(a) was significantly ($P<.05$) higher in females than males, but the logistic regression analysis showed significant association of Lp(a), LDL-C, and duration of diabetes mellitus (DM) with CHD in male patients only. Although female patients with CHD and macroalbuminuria had significantly ($P<.05$) higher Lp(a) than normoalbuminuric female patients without CHD, no such association was found in males and no significant association was found between Lp(a) and the degree of albuminuria. Partial correlation analysis controlling for age, sex, and BMI showed significant correlation of Lp(a) with total cholesterol only ($P=.03$) and no correlation was found with other lipid parameters. Multiple regression analysis did not show significant associations of Lp(a) with standard CHD risk factors, HbA(1c), and plasma creatinine. This study is in agreement with studies in other populations, which showed that Lp(a) may not be an independent risk factor for CHD in patients with DM. However, as Lp(a) could promote atherogenesis via several mechanisms, follow-up studies in our patients will confirm if increased Lp(a) concentration can partly account for the poorer prognosis when diabetic patients develop CHD.

Retinopathy of Prematurity: Mutations in the Norrie Disease Gene and the Risk of Progression to Advanced Stages

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Background: Retinopathy of prematurity (ROP) is a retinal vascular disease that occurs in infants with short gestational age and low birth weight and may lead to retinal detachment and blindness. Missense mutations in the Norrie disease (ND) gene have been associated with the risk of progression to advanced stages in cases of ROP from the US and also in clinically similar ND and familial exudative vitreoretinopathy.

Methods: We have screened two ND gene mutations, namely A105T and Val60Glu, by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and allele-specific PCR methods, respectively, in 210 Kuwaiti premature newborns to replicate these findings in a different ethnic group.

Results: In the Kuwaiti premature newborn cohort, 115 of 210 babies had no eye problems and served as controls, while 95 were cases of ROP. In 71 of 95 ROP cases, the disease regressed spontaneously on or before stage 3, while in 24 of 95 ROP cases the disease progressed to advanced stages 4 and 5. In case of missense mutation (A105T), the AA genotype was detected in 96% of controls compared with 87% of ROP cases (NS); similarly no significant difference was found between spontaneously regressed ROP cases and those who progressed to advanced stages. For the Val60Glu mutation, no significant association was detected between the genotype and progression of ROP to advanced stages.

Conclusion: Unlike data from the US, our findings from a Kuwaiti cohort of ROP cases and controls suggest a lack of association between the two ND gene mutations (A105T and Val60Glu) and ROP and the risk of progression of the disease to advanced stages.

Incidence and Seasonal Variation of Type 1 Diabetes in Children in Farwania Area, Kuwait (1995-1999)

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The aim of our study was to confirm the continuing rise in the incidence of Type 1 diabetes among Kuwaiti children aged 0-14, and to assess the effect of seasonality on incidence. Data from all newly diagnosed diabetic children between the period of 1995 and 1999 were analyzed. A total of 129 cases of Type 1 diabetes were diagnosed during the study period, of whom 68 were Kuwaiti nationals and were included in the study. The incidence was 20.18 per 100000 (95% CI 16.3-28.2). Incidence rates for the age-groups 0-4, 5-9 and 10-14 were 8.12, 21.07 and 34.06, respectively. There was a significant female predominance (F:M ratio was 1.4:1, $P < 0.05$). More cases were diagnosed in the cool months (November-February) compared with the warm months (June-September, $P < 0.05$). There was increase in incidence from 1995 to 1999, but compared with data from the 1980s on the same age group, incidence has increased. A positive family history of Type 1 diabetes in a close relative was recorded for 30% of the patients. Although, only data from one hospital were included, Kuwait is very small geographically and not likely to have differences between different areas. Stress factors, economic growth, changes in the nutritional habits and the adoption of the western lifestyle may explain some of this increase.

Predictors of Coronary Disease in Patients with End Stage Renal Disease

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Patients with end stage renal disease have a high prevalence of cardiovascular disease and coronary arteriography is often routinely performed prior to kidney transplantation. However, the value of the conventional risk factors and non-invasive markers of coronary artery disease (CAD) in triaging patients for coronary arteriography has not been fully examined. 116 patients with end stage renal disease were evaluated. Coronary arteriography was performed in all patients either for a suspicion of CAD or as part of a routine pre-transplant evaluation. Lesions causing $>$ or $=$ 50% luminal diameter stenosis in any of the three major coronary artery systems were considered significant. The mean age was 53.3 ± 9.3 years. Significant CAD was present in 69 patients (60%). Increasing age, family history of premature ischemic heart disease, the presence of angina, abnormal Q waves on the ECG or abnormal ST segment depression and the presence of coronary calcification were significant markers of coronary artery disease. However male gender, diabetes mellitus and obesity did not correlate with coronary disease. Even though hypertension, hypercholesterolemia and smoking were also not useful predictors these could have been modified by the renal failure. In conclusion increasing age, a family history of premature ischemic heart disease and some non-invasive markers were useful predictors of coronary disease.

Effectiveness of Laparoscopic Fundoplication for Gastro-Oesophageal Reflux

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Background: Gastro-oesophageal reflux (GERD) is a common condition. Many patients respond to conservative therapy. Severe symptomatic cases and those who fail medical treatment are referred to surgery. The long-term results of open fundoplication surgery have been good with a more than 90% response after 10 years of follow-up. The introduction of laparoscopic fundoplication achieved the same results with shorter hospital stay, a better cosmetic result and less cost to the health care providers.

Patients and Methods: 74 patients who failed medical treatment for GERD were treated by laparoscopic fundoplication. The Toupet procedure was performed in 66 of these patients, the others patients had a Nissen-type fundoplication. The patients were followed up for a mean period (\pm SD) of 14.8 ± 8.8 months (range 3-33 months).

Results: Most of the patients were males ($n = 65$). The mean age (\pm SD) of all the patients was 36.1 ± 9.5 years (range 17-60 years). The majority (93.8%) reported disappearance of symptoms and are not using any antireflux medications. Five patients (6.7%) are considered failures of the procedures. Of these, three patients developed recurrence of reflux symptoms during the follow-up period. The other two patients developed complications, i.e. gas bloat, persistent vomiting and dysphagia which warranted taking down the wraps laparoscopically. Two patients developed a small incisional hernia at the site of the 10 mm port. The mean of hospital stay (\pm SD) was 3.1 ± 1.3 days (range 1-7 days).

Conclusion: Laparoscopic fundoplication is safe and effectively relieves reflux symptoms in patients who fail medical treatment.

Pre- and Postnatal Tissue Selenium of the Rat in the Growing State

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The aim of this study is to quantify the selenium (Se) content (in microg/g) during different gestational periods in rat fetal tissues, and to follow up the changes in the Se content of the placenta, fetal head, liver and lung during gestation and postpartum periods. Locally reared virgin female Wistar rats were mated. Pregnant rats were sacrificed on days 15, 18 and 21 of pregnancy. Newborn pups at the age of 3 days and rats at the age of 1 month were also investigated. There was a gradual increase in placental and whole head Se content as gestation proceeded compared to day 15; however, the differences between the groups were not statistically significant. The liver Se content at day 18 of gestation was significantly higher than at day 21 of gestation and in rats at 3 days of age, but lower than the Se content of the liver of rats at the age of 1 month and the differences were statistically significant. The lung Se content was higher at day 18 of gestation than at day 21 and in the 3-day-old rats, and all differences between all groups were statistically significant except when the lung Se content at day 18 is compared to that of 1-month-old animals. The continuous increase in the Se content of the placental tissues and the whole head, although not significant statistically, may indicate that the fetus relies heavily on its supply of Se from the maternal blood and in part on the supply of thyroid hormones which are important for brain development, as evidence exists that T(4) and T(3) are present in the fetal brain in early fetal life before the onset of fetal thyroid function. The higher content of Se on day 18 and its decline on day 21 of gestation in the liver may imply that it is stored and being utilized partly in other tissues for other functions and particularly for thyroid hormone synthesis, metabolism and functions.

Blood Purine and Energy Status in Rats with Colitis

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Colitis reduces the blood and tissue levels of adenosine deaminase and adenylyate deaminase. Whether this has any effect on blood purines remains to be determined. The aim of this study was to measure the adenylyate pool, substrates of the above enzymes, and energy status in blood from rats with colitis. Colitis was induced by intrarectal administration of acetic acid and followed over a period of seven days. The levels of ATP, ADP, AMP, adenosine, inosine, and uric acid were analyzed by HPLC, and energy status was estimated. Myeloperoxidase was used as a marker of colitis. Concentrations of ATP, ADP, AMP and adenosine decreased during days 1-5, whereas energy status decreased on day 2. The concentrations of inosine, uric acid, and hemoglobin remained unaltered, whereas colonic myeloperoxidase activity increased. These findings demonstrate colitis-induced reduction of the circulating purines, which may be due to their enhanced usage for the repair of the inflamed colon.

Angiotensin Converting Enzyme Gene Insertion/Deletion Polymorphism in Idiopathic Nephrotic Syndrome in Kuwaiti Arab Children

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Objective: Angiotensin converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism influence the circulating and cellular levels of ACE and has been shown to be a risk factor in a number of diseases including IgA nephropathy. We have investigated the association of ACE gene I/D polymorphism with the clinical presentation of idiopathic nephrotic syndrome (INS) in Kuwaiti children.

Materials And Methods: The genotypes for ACE gene I/D polymorphism were determined in 102 subjects (54 INS cases and 48 healthy controls) using a PCR method.

Results: The distribution of DD, ID and II genotypes was 70%, 20% and 10% in INS cases compared with 52%, 46% and 2% in the controls. The mean age of onset of the disease was significantly lower in the INS cases with DD genotype (37 months) compared with cases with II genotype (65 months, $p < 0.05$). The clinical manifestation of the disease was considerably severe in cases with DD genotypes compared with cases having ID and II genotypes. The INS cases with DD genotype also showed a significantly higher incidence of steroid sensitivity and steroid dependence. Seventy-three per cent of the INS cases with minimal change lesion had a DD genotype. Also 70% of the cases which needed cytotoxic drugs had DD genotype. **Conclusion:** Our data suggest an association of the D-allele of the ACE gene I/D polymorphism with the clinical manifestation of INS in Kuwaiti Arab children.