Faculty of Medicine

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Title: Molecular Events Associated With Underlying Changes Of The Vascular Endothelium And Subendothelial Space During Atherogenesis In An Animal Model
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Title: Determinants Of Health Related Quality Of Life Among Type 2 Diabetic Patients Attending National University Of Malaysia Medical Centre
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Title: Effect Of Exogenous Leptin On Blood Pressure, Urinary Protein Excretion, Endothelial Activation And Ace2 Expression During Pregnancy In The Rat
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Diabetes Mellitus is notorious for its metabolic effect, acute and long term complications and impact on Quality of Life (QOL). Plethora of literature has documented the negative impact of DM on QOL. Currently, religion and spirituality constitute a topic of great importance to most of the world’s population where researchers have notably focused attention on the relationship between religion, spirituality and Quality of Life (QOL). However there is little, if none is known about the relationship of spirituality and diabetes-related QOL. The primary aim of this study was to determine factors affecting QOL among sample of patients with type 2 diabetes mellitus attending the medical centre of National University of Malaysia, Kuala Lumpur, Malaysia specifically in relation to spirituality. For this purpose we had to translate the English version of Spiritual Wellbeing Scale (SWBS) into Malay language as well as validate the Malay version of SWBS among Malaysian general population at Klang Valley and thence we proceeded to measure diabetes-related QOL among diabetic patients at the National University of Malaysia Teaching Hospital. Two questionnaires were used in this study; the Malay version of Spiritual Wellbeing Scale and the Audit of Diabetes Dependent Quality of Life (ADDQOL-18). The Malay SWBS is made of 20 items rated on 6 point Likert scale. The ADDQOL-18

Raised leptin levels have been reported in placentae and serum of women with elevated blood pressure and proteinuria during pregnancy. The role of leptin in this however remains unclear. ACE2 is a new member in RAAS, which is reported to have hypotensive and anti-inflammatory effect and its suppression leads to increased blood pressure and endothelial activation. Therefore, this study investigated the effect of leptin and xanthenone (ACE2 activator) administration on systolic blood pressure (SBP), proteinuria and serum markers of endothelial activation during pregnancy in Sprague-Dawley rats. Eighty female Sprague-Dawley rats, aged 12-13 weeks were randomised into 10 groups, Group 1 acted as a control non-pregnant group and given saline (NSNP). Group 2, control pregnant rats, was given saline (NSP), group 3 was given 60 μg / kg /day of leptin starting from the 1st day of pregnancy (LD1-60), group 4, was given 60 μg / kg /day of leptin starting from the 10th day of pregnancy (LD10), group 5, given leptin from day 16 of pregnancy (LD16). Group 6 (L14D-60), given

The development of atherosclerotic plaques is a multistep process involving changes in blood lipid composition, dysfunction of the endothelium, and infiltration of inflammatory cells. Cellular and molecular studies revealed enhanced expressions of several genes in development of atherosclerosis. This thesis aimed to investigate whether changed expressions of endothelial surface genes (VCAM, ICAM, and selectins), MCP-1, MMPs, and tissue inhibitor of MMPs (TIMPs) are associated with the underlying changes of the endothelium and subendothelial space in the development of atherosclerosis. In addition, the present study also determined whether any novel differentially expressed gene (DEG) is associated with atherogenesis. Rabbits were fed with 1 % cholesterol to induce atherosclerosis. Blood serum was collected for lipid profile analysis. Aorta tissues were used to study changes in morphology, ultrastructure, and gene expressions. Luminal endothelial surface from rabbit aortic tissue was examined by scanning electron microscopy (SEM) using low vacuum mode. The tissue cross-sections were stained with hematoxylin and eosin (H&E) for microscopic observations of intimal thickening. Total RNA was extracted from aorta tissues for gene expressions analysis. Differentially expressed genes (DEG), were analyzed by Real-time polymerase chain reaction (PCR) and Quantigene® Plex. Annealing
is composed of two overview items and 18 life domains which are rated for both impact of diabetes and importance to diabetic patients. Data for the validation phase were collected from 623 Malaysians from three main ethnic groups in Klang valley by trained enumerators. Data for measuring diabetes-related QOL was collected by trained research assistant from 256 patients with type 2 DM who were attending diabetes clinic at the National University of Malaysia Medical Centre. Descriptive statistics were produced for all study variables. Exploratory factor analysis with promax rotation was used to explore the factor structure of the Malay SWBS and determine the reliability coefficient. Stepwise multiple linear regression was used to identify factors associated with diabetes QOL. The results of the study showed an equivalent translated version of the Malay SWBS. The validity of the Malay SWBS was ascertained with the findings of three factors model explaining 59.70% of the total variance, and a reliability coefficient of more than 0.7. Diabetic patients had high proportion of diabetes complications, poor glycemic control, hypertension and obesity. The QOL among diabetic patients in this study was negatively affected. Multiple linear regression showed that glycaemic control (HbA1c), diabetes worry, use of insulin, more than 10 years’ duration of diabetes, neuropathy and retinopathy were associated with poor quality of life, whereas being satisfied with waiting time for consultation and being spiritually affiliated, were associated with better QOL. We concluded that the QOL among the study sample was negatively affected by diabetes. Measures to reduce diabetes complications through better glycemic control and well-tolerated treatment modality, and reducing waiting time would go a long way to improve the quality of life. The positive relation of spirituality to QOL among diabetic patients opens new vista for further research in the field.

leptin approximately 14 days before pregnancy, Group 7 was non-pregnant rats receiving leptin for a period of 20 days (LNP). Group 8, given 60 μg / kg/day of leptin with 600 μg / kg/day of xanthenone (XNT), an ACE2 stimulant from day 1 of pregnancy (L+ACE2a), while group 9 was given 600 μg / kg/day of XNT alone starting from day 1 of pregnancy (ACE2a). Group 10 was given 120 μg / kg/day of Leptin starting from day 1 of pregnancy (LD1-120). SBP, serum ACE, ACE2, endothelin-1, E-selectin and ICAM-1 levels were estimated. ACE2, endothelin-1, E-selectin and ICAM-1 gene expressions were determined in the kidney and aorta. Data were analysed using ANOVA and post-hoc analysis, data are presented as mean ± S.E.M. Compared to group 1, SBP was higher in the lepion only treated group (P<0.001) and lower in rats treated with xanthenone alone (P< 0.01). ACE2 activity and expression were lower in leptin only treated rats (P<0.05). Urine protein excretion, serum endothelin-1, serum E-selectin, and ICAM-1 levels were significantly higher than controls in leptin only treated rats (P<0.05) but not in the others. It seems, leptin administration during pregnancy significantly increases SBP, urinary protein excretion, levels and expression of markers of endothelial activation, but decreases the level and expression of ACE2. These effects are prevented by xanthenone, implicating the role of ACE2 in leptin-induced raised blood pressure and proteinuria during pregnancy. However, further studies are required to examine the underlying mechanism responsible for this and its relevance to preeclampsia in humans.

control primer (ACP)-based GeneFishing™ PCR was used to analyze differentially expressed unknown genes. The DNA fragment from DEG was cloned, sequenced, and validated by Real-time PCR. Presence of highly expressed MMP genes in the intimal thickening of atherosclerotic tissues was detected using immunohistochemistry (IHC) staining. Lipid profiles obtained from rabbits fed with 1 % cholesterol showed highly significant difference (p < 0.001) in total cholesterol and low density lipoprotein (LDL) while terminating the study at week-2 and week-8. Ultrastructural observations of the aortic luminal surface by low vacuum mode SEM showed changes from normal regular smooth intact endothelium to irregular luminal surface including endothelial swelling and formation of ‘craters’ on the endothelial surface. In the present study, we examined the aorta tissues much closer to its natural conditions using a preparation not subjected to critical drying point and heavy metal coating. Ultrastructural changes of the luminal surface in atherogenesis indicate dysfunction of the endothelium. Higher expression of VCAM, P-selectin, E-selectin, and chemokine (MCP-1) might influence structural integrity of the luminal endothelium. H&E stained aorta tissues exhibited discernible intimal thickening at week-8 of atherogenesis; the tissues were found to be consisted of abundant foam cells. MMPs and TIMPs showed different expression profiles in Real-time PCR and QuantiGene® Plex assays. Highest MMP-12 expression was detected by both assays at week-8 atherogenesis. IHC staining of the foam cells detected expressions of MMP -1, -3, and -12 in week-8 aorta tissues. We identified DEG detected from ACP-41 as cathepsin B gene; it was highly expressed at week-8 and week-12 of atherogenesis. Based on the findings of the present study, we can conclude that loss of endothelium integrity is associated with higher expressions of several types of endothelial surface genes. Additionally, we also found that intimal thickening was associated with differential expression profiles of MMPs and TIMPs genes. We also identified Cathepsin B as proatherogenic.