Original Research – Prediabetes/Diabetes Mellitus

Effects of *Stevia rebaudiana bertoni* on Bone Turn Over Factors and Bone Marrow Density in Diabetic Rats

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Introduction. Diabetes mellitus results in an increased risk of developing osteoporosis. *Stevia rebaudiana bertoni* is a herbal medicine with hypoglycemic and antioxidant effects in diabetic animals. We aimed to assess the effects of aquatic extract of *Stevia rebaudiana bertoni* on bone mineral density (BMD) and bone turn over factors and lipid peroxidation in diabetic rats

Methodology. 40 Wistar rats 220-240 days old were randomly assigned to five groups, receiving different substances by gavage; Group 1: Normal control that received normal saline; Group 2: Normal control that received 200 mg/kg/day *Stevia* extract; Group 3: Diabetics control that received normal saline; Group 4: Diabetics rats that received 400 mg/kg/day *Stevia* extract; Group 5: Diabetics rats that received 2.7 mg/kg/day pioglitazone. Fasting blood glucose, calcium, phosphate, serum bone-specific alkaline phosphatase (BALP), serum level of osteocalcin, C-telopeptide of collagen (RatLaps) and malondialdehyed (MDA) were measured six weeks after intervention.

Results. The BMD of the tibia decreased significantly in diabetic rats after 6 weeks while a significant increase was observed in the BMD of the tibia in diabetic rats that had received aquatic extract of *Stevia rebaudiana bertoni* after 6 weeks. Rat laps increased in all diabetic rats and no treatment could decrease it. Alkaline phosphatase and phosphor concentrations were higher among diabetic rats. Osteocalcin and Serum calcium level decreased in diabetic rats, which was restored to normal using *Stevia*. Diabetes resulted in a significant increase in Serum MDA concentration compared to the control group. Gavage feeding of *Stevia* restored serum MDA level ($P<0.05$). Aquatic extract of *Stevia* decreased MDA levels in the control group as well. Pioglitazone treatment in diabetic rats did not change MDA level.

Conclusions. The prevention and treatment of diabetic osteopenia could, in part, be helped by *Stevia rebaudiana bertoni.*

Keywords: Stevia, diabetes, osteoporosis, bone mineral density, osteocalcin

Original Research – Prediabetes/Diabetes Mellitus

Risk of Developing Type 2 Diabetes Mellitus or Impaired Fasting Glucose in Night Shift Workers

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Introduction. Several studies have investigated the incidence of impaired glucose metabolism in shift workers. Some studies have pointed to a positive association between the two, others have shown that there is no significant difference in the glucose levels of day and night shift workers. This study aims to review published prospective or retrospective population-based studies and to determine if over-all evidence supports the association between night shift work and the risk of impaired glucose metabolism.

Methodology. A systematic search of PubMed and Cochrane was done with restriction for published studies in English. Studies were included if follow-up was at least 2 years and had an assessment of sleep schedules in both dayshift and nightshift workers at baseline and markers of glucose metabolism as outcome (FBS, HbA1C). Relative risks (RRs) were extracted with 95% CI and pooled using random-effects models. Sensitivity analysis was performed; heterogeneity and publication bias were assessed.

Results. There was a statistically significant difference between the two groups, favoring night shift workers with increased risk for diabetes mellitus or impaired fasting glucose (1.45 [1.20, 1.76], $P < 0.05$) compared to dayshift workers.

Conclusions. Nightshift work is associated with an increased risk of developing impaired fasting glucose or diabetes mellitus. The impact of night shift work on the development of diabetes mellitus is significant and should certainly be addressed by government and private companies.

Keywords: nightshift workers, Type 2 diabetes mellitus, impaired fasting glucose

Original Research – Prediabetes/Diabetes Mellitus

Effect of Cholecalciferol on Expression of GLUT 4 in Adipocytes of Diabetic Rats

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Introduction. Cholecalciferol may have a role in improving diabetes mellitus. However, studies on the mechanism and dose exploration of the cholecalciferol are still unclear and require further investigation. This study was to examine the effect of cholecalciferol on blood glucose, diameter of adipocyte and expression of glucose transporter (GLUT) 4 in adipocyte of diabetic rats.

Methodology. Nineteen male diabetic rats of Wistar strain were divided into 4 groups (K, X1, X2, and X3) used in this study. In order to induce diabetes mellitus, the animals were fed high fat diet for 3 weeks, and administered a single intraperitoneal injection of streptozocin (35 mg/kg) at the end of the second week. Cholecalciferol were administered 6.25 mcg/kg in X1, 12.5 mcg/kg in X2, and 25

mcg/kg in X3 per oral, once daily, for 14 days, while propylene glycol as placebo was administered in group K. Twenty four hours from the last treatment, blood glucose was measured, then the animals were sacrified. Subcutaneous adipose tissues were processed into histological preparation with routine and immunohistochemical staining. Data were analyzed with one way ANOVA test (α= 0.05).

Results. There were no significant difference in blood glucose (p=0.199) and diameter of adipocyte (p=0.218) between groups. There was significant difference of GLUT 4 expression in adipocyte (p=0.035) between groups, where the differences were found between group K and groups X1, X2, and X3.

Conclusions. Cholecalciferol can increase the expression of GLUT 4 in adipocyte without followed by alteration of blood glucose and diameter of adipocyte of diabetic rats.
Keywords: cholecalciferol, GLUT 4, adipocyte, diabetes

Original Research – Prediabetes/Diabetes Mellitus

Differencial Expression and Role of Hyperglycemia-Induced Oxidative Stress in Epigenetic Regulation of Beta Adrenergic Receptors in Retinal Endothelial Cells*

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Introduction. Aberrant epigenetic profiles are concomitant with a spectrum of developmental defects and diseases. Role of methylation is an increasingly accepted factor in the pathophysiology of diabetes and its associated complications. This study aims to examine the correlation between oxidative stress and methylation of β1, β2 and β3-adrenergic receptors and to analyze the differential variability in the expression of these genes under hyperglycemic conditions.

Methodology. Human retinal endothelial cells were cultured in CSC complete medium in normal (5 mM) or high (25 mM) glucose to mimic a diabetic condition. Reverse transcription PCR and Western Blotting were performed to examine the expression of β1, β2 and β3-adrenergic receptors. For detections, immuno-cytochemistry was used. Bisulfite sequencing method was used for promoter methylation analysis. Apoptosis was determined by the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay. Dichloro-dihydrofluorescein diacetate (DCFH-DA) assay was used to measure reactive oxygen species (ROS) production in the cells.

Results. β1 and β3-adrenergic receptors were expressed in retinal endothelial cells while β2-adrenergic receptor was not detectable both at protein and mRNA levels. Hyperglycemia had no significant effect on β1 and β2-adrenergic receptors methylation and expression however β3-adrenergic receptors showed a significantly higher expression ($p < 0.05$) and methylation ($p < 0.01$) in high and low glucose concentration respectively. Apoptosis and oxidative stress were inversely correlated with β3-adrenergic receptors methylation with no significant effect on β1 and β2-adrenergic receptors. β2-adrenergic receptor was hypermethylated with halted expression.

Conclusion. Our study demonstrates that β1 and β3-adrenergic receptors expressed in human retinal endothelial cells. Oxidative stress and apoptosis are inversely proportional to the extent of promoter methylation, suggesting that methylation loss might be due to oxidative stress-induced DNA damage.

Keywords: expression, methylation, ROS, adrenergic receptors, retinal endothelial cells

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Original Research – Metabolic Bone Disease

Physical Performance Test as a Predictor of Osteoporosis and Fragility Fracture in Chungju Metabolic Disease Cohort (CMC) Study

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Introduction. Diminished physical performance can be detrimental, causing falls and subsequent fractures. However, it is unclear whether the decline in bone mineral density (BMD) can be explained by functional ability changes. The purpose of this study was to investigate if physical performance test can predict fracture, independent of BMD and other risk factors in postmenopausal women.

Methodology. This study was carried out from 2007 to 2011 among adults included in the Chungju Metabolic Disease Cohort (CMC) study. Among 3741 postmenopausal women (67.6±8.1 years old) who underwent DXA, 669 women who had taken anti-osteoporotic drugs were excluded. The fracture events were determined using a standardized questionnaire. Measures of physical performance included one-leg-stance time (OLST), Get-Up-and-Go Test (GUGT).

Results. 53.7% of women had osteoporosis and 17.0% had history of fragility fracture. GUGT performance could predict BMD of trochanter (R2=0.402, p<0.01) and total hip (R2=0.430, p<0.05) when controlling for covariates. However OLST could not predict BMD at any site. When evaluated in quartiles, decreasing performance in OLST or GUGT was the risk factor for fragility fracture. However, after adjusting for age, T-scores at all measurement sites (femur neck, trochanter, total hip, L-spine), number of

pregnancy, and history of fall were the risk factors for fragility fracture.

Conclusions. GUGT performance can be a validated predictor for BMD of trochanter and total hip fracture in postmenopausal women. Additionally, subjects who had slow GUGT or short OLST test performance are at high risk of fragility fracture. However, age, BMD, number of pregnancy, and history of fall are more important factors for fracture prediction than GUGT or OLST in postmenopausal women.

Keywords: postmenopause, fracture, risk, bone mineral density

Original Research – Thyroid Diseases

Classification Using Number of Involved Cervical Lymph Nodes is Useful in Predicting Persistent/Recurrent Disease in Patients with Papillary Thyroid Carcinoma

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Introduction. Recent studies demonstrate that risk of recurrence in patients with cervical lymph node (LN) metastasis of papillary thyroid carcinoma (PTC) can vary depending on characteristics of metastatic LNs, especially the number of involved LNs. The aim of this study is to evaluate the efficacy of the classification based on the number of involved LNs in Korean PTC patients.

Methodology. This study included patients who underwent their initial thyroid surgery with subsequent radioactive iodine remnant ablation therapy due to classical PTC between 2004 and 2007 at Asan Medical Center in Korea. We excluded patients who have large primary tumor (> 4cm), gross extrathyroidal invasion or distant metastases at presentation.

Results. A total of 1,352 patients were eligible for analysis. Of them, 514 (38%) were pN0/Nx, 610 (45%) had ≤ 5 LN metastases (low volume N1 disease) and 228 (17%) had > 5 LN metastases (large volume N1 disease). The ablation success rate and the risk of recurrence or persistent disease were significantly different between groups (92% of ablation success rate, 1% of the risk of recurrent or persistent disease in pN0/Nx, 82%/7% in low volume N1 disease and 54%/21% in high volume N1 disease). The sub-classification of high volume N1 disease with the cutoff point of the number of involved LNs as 10, also worked. Patients with >10 LN metastases (93, 41% of high volume N1 disease) had 48% of ablation success rate with 31% of the risk of recurrent/persistent disease.

Conclusions. The classification based on the number of involved LNs clearly predicts the ablation success rate and the risk of recurrent/persistent disease in Korean PTC patients. To differentiate N1 PTC disease using the number of involved LNs is appropriate for assessing the risk of recurrence.

Keywords: papillary thyroid cancer, lymph node metastasis, recurrence, persistent disease

Original Research – Thyroid Diseases

The Effectiveness and Mechanism of Preoperative Lugol Solution for Reducing Blood Flow in Euthyroid Patients with Graves' Disease

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Introduction. In order to reduce intra- and post-operative complications, preoperative Lugol's solution in Graves' disease has been known to 1) rapidly decrease thyrotoxicosis and 2) decrease the vascularity of the thyroid gland. The effect and mechanism of Lugol solution for decreasing the blood flow has not yet been investigated in euthyroid patients with Graves' Disease.

Methodology. 25 euthyroid patients with Graves' disease admitted for preoperative Lugol's solution for 10 days were included in this study. We measured the following parameters before Lugol's solution administration and on the day of operation: 1) Thyroid blood flow (of superior thyroid artery, 2) Systemic angiogenic factor (VEGF), and 3) Systemic inflammatory factor (IL16).

Results. Blood flow, serum VEGF, and serum IL16 were significantly decreased 10 days after taking Lugol solution ($p<0.0001$). The average dropping rates were 40%, 55% , and 60% for blood flow (0.29 vs 0.17 L/min; $p< 0.001$), serum VEGF (0.020 vs 0.009 pg/mL; $p=0.0009$), and Serum IL16 (8340 vs 3725 pg/mL; $p=0.0094$), respectively.

Conclusions. We conclude that Lugol's solution very effectively reduces the blood flow, angiogenic factor (VEGF), and inflammatory factor (IL16) in euthyroid patients with Graves' disease. Preoperative use of Lugol solution is highly advocated for all patients with Graves' disease.

Keywords: Lugol's solution, Graves' Disease

Original Research – Thyroid Diseases

BRAF V600E Mutation Status and Clinical Implication in Histological Variants of Papillary Thyroid Carcinoma

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Introduction. The aim of this study was to investigate BRAF mutation status based on the histological variant of papillary thyroid carcinoma (PTC) and to determine the significance of BRAF V600E mutation in follicular variant of PTC (FVPTC) in Korean patients.

Methodology. In all, 691 PTC cases were classified to each histological variants. BRAF mutation analysis was performed routinely using multiplex PCR by applying dual priming oligonucleotide(DPO). Clinicopathological characteristics were compared between BRAF V600E mutation-positive and -negative groups in FVPTC.

Results. The classic type, FVPTC, diffuse sclerosing variant, and tall cell variant represented 656(94.9%), 24(3.5%), 7 (1.0%) and 4 (0.6%), respectively. The classic type, FV, DSV, and TCV harbored 300(45.7%), 9(37.5%), 1 (14.3%) and 2 (50%) in BRAF V600E mutation, respectively. The BRAF mutation-positive FVPTC was marginally associated with larger tumor size (P = 0.067) and old age (P = 0.052) due to small sample size. However, there was no significant association in extrathyroidal extension, multifocality, lymphovascular invasion, lymph node metastasis and higher (III/IV) TNM stages.

Conclusions. BRAF V600E mutation in FVPTC was not uncommon and it may be a potential prognostic factor as it is in classical PTC. However, further studies with a larger patient population and extended follow-up period may be required for verification of prognostic predictors.

Keywords: BRAF, papillary thyroid cancer

Original Research – Thyroid Diseases

The Impact of Subclinical Thyroid Dysfunction on Coronary Vasospasm in Patients Without Associated Cardiovascular Risk Factors

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Introduction. Subclinical hypothyroidism is associated with endothelial dysfunction and impaired coronary flow reserve. However, the effect of subclinical thyroid dysfunction or thyroid autoimmunity on variant angina has not been cleared yet.

Methods. Among 414 consecutive patients, who underwent coronary angiography with ergonovine provocation test (EPT) without associated cardiovascular risk factors, 177 with positive EPT [EPT (+)] and 237 with negative EPT [EPT(-)] were studied. Subclinical hypothyroidism was defined as a thyroid-stimulating hormone (TSH) level > 4.0 mIU/l and a normal free thyroxine level (0.89-1.76 ng/dl); and subclinical hyperthyroidism was defined as a TSH level < 0.45 mIU/l and a normal free thyroxine level. We excluded the patients with the presence of fixed organic stenosis. The relationship between coronary artery spasm and the presence of subclinical thyroid dysfunction as well as serum thyroidperoxidase autoantibody (TPO Ab) was evaluated.

Results. The proportion of subclinical hypothyroidism in patients with EPT (+) was significantly higher than in the patients with EPT(-)(17% vs. 10%, p=0.023). However, there was no significant difference in the proportion of subclinical hyperthyroidism between the groups. Moreover, patients with EPT (+) showed more positive TPO Ab (31% vs. 13%, P<0.0001) than those with EPT (-). There was a positive correlation between EPS (+) and TPO positive (r=0.226, p<0.001), subclinical hypothyroidism (r=0.112, p=0.033), and body mass index (r=0.123, p=0.018). Multiple linear regression analysis revealed that the only significant predictors of EPT (+) were body mass index(standardized β coefficient=0.108, p=0.024) and the presence of TPO Ab (standardized β coefficient =0.205, p<0.001) after adjustment for traditional risk factors.

Conclusions. Subclinical hypothyroidism, not subclinical hyperthyroidism, is associated with coronary spasm as established by ergonovine test. Presence of TPO Ab is significantly associated with increased coronary vasospam in patients without cardiovascular risk factors.

Keywords: subclinical hypothyroidism, ergonovine provocation test, coronary vasospasm, autoimmunity

Original Research – Thyroid Diseases

Risk Factors for Recurrence after Treatment of Micropapillary Thyroid Cancer: Philippine General Hospital Experience

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Introduction. Papillary thyroid microcarcinoma is papillary thyroid carcinoma which measures less than or equal to 1.0 cm size. Although it has a low mortality, locoregional recurrence is common and independent prognostic factors for recurrence have not been clearly defined.

Methodology. Clinicopathologic variables predicting PTMC recurrence were determined by a retrospective analysis of 117 patients. Multivariate logistic regression analyses were used to determine significant predictors of tumor recurrence.

Results. Of the 117 patients with MPTC, 19 (16.3%) had recurrence with a median time to recurrence of 33 months. Multivariable logistic regression analysis showed that age >45 years at time of diagnosis [HR=3.59], smoking [5.08], alcohol intake [4.92], concomitant Graves' disease [4.61], multifocality [3.75], bilaterality [4.33], lymph node involvement at presentation [7.15] and presence of distant metastasis at presentation [6.48].

Conclusions. Papillary thyroid microcarcinoma in our institution has a higher recurrence rate. Lymph node metastasis at presentation was the most important risk factor associated with recurrence. The recognition of these

risk factors will help us in identifying patients that will require more intensive treatment and closer follow-up.

Keywords: papillary thyroid microcarcinoma, thyroid cancer

Original Research – Thyroid Diseases

Clinical and Surgical Outcomes of Patients who Underwent Robot-Assisted Thyroidectomy for Benign and Malignant Thyroid Nodules in a Tertiary Hospital

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Introduction. Robot-assisted thyroidectomy is being performed in different parts of the world since it was first described in 2008. However, this procedure is not routinely being done in our country. This study aims to report the clinical and surgical outcomes of patients who underwent robot-assisted thyroidectomy for benign and malignant thyroid nodules in a tertiary hospital.

Methodology. This is a retrospective study from May 2011 to July 2013. Data were obtained from the Census for Robot-Assisted Thyroidectomy of St. Luke's Medical Center, Global City. Data were collected using percentages and proportions.

Results. Among the 9 patients, 4 or 44.4% underwent total thyroidectomy, 5 had subtotal thyroidectomy. Seven or 77.8% subjects had benign final histopathalogic result, 2 were malignant, both of which were Papillary Thyroid Carcinoma. No subject had post-operative hypocalcemia. The average number of post-operative analgesics for pain control was 3. The lowest number of post-operative analgesic was 2, the highest was 5. The length of hospital stay, on the average, was 2.67 days + 0.87. The shortest stay was 2 days, while 4 days was the longest hospital stay. The mean operating room (OR) time was 3.21 hours + 1.54. The fastest OR time was 1.5 hours, the longest was 6.42 hours. There was no conversion from robot-assisted thyroidectomy to conventional thyroidectomy. **Conclusions.** This study shows that robot-assisted thyroidectomy has acceptable clinical and surgical outcomes and is an option for patients undergoing surgery for both benign and malignant thyroid nodules.

Keywords: robot-assisted thyroidectomy, thyroid nodule

Original Research – Lipid/Cardiovascular Disorders/Hypertension

Lipodystrophy and Insulin Resistance in HIV-Infected Patients Treated with Anti-Retroviral Therapy

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Introduction. ART-associated lipodystrophy is not only a morphologic change but frequently is associated with profound metabolic disturbance in glucose and lipid metabolism.

Methodology. This is a case-control study aimed to compare the metabolic abnormalities, the proportion of metabolic syndrome, insulin resistance and the CVD risk between patients with and without lipodystrophy. The subjects were 99 patients with lipodystrophy and 99 sex, age and BMI-matched patients without lipodystrophy. The study was conducted at Specialist Hospital Mingaladon, Yangon, from January 2012 to July 2013. Lipodystrophy diagnosis was a clinical one, reported by the patients and confirmed by the researcher. Metabolic syndrome diagnosis was made by ATP III criteria, insulin resistance was calculated by HOMA2-IR calculator and 10-year CVD risk was estimated by Framingham global CVD risk calculator (2008).

Results. Patients with lipodystrophy had significantly higher fasting insulin, HOMA2-IR values (2 vs 1.5, p=0.014), triglyceride, and lower HDL levels than those without it. Fasting blood sugar, total and LDL-cholesterol, prevalence of metabolic syndrome (33% vs 22%, p=0.08) and 10-year CVD risk (4.8% vs 4.3%, p=0.53) were not significantly different. Lipoatrophic type was the commonest phenotype (62%) and lipohypertrophic type was the metabolically worst phenotype. Lipodystrophy was significantly associated with insulin resistance (p=0.05), but after exclusion of metabolic syndrome, the association was no more significant (p=0.13). In logistic regression analysis, the risk of insulin resistance was about 2-fold higher in patients with lipodystrophy than those not having it (OR=1.98, 95% CI=1.04-3.76, p=0.037). **Conclusions**. Patients with lipodystrophy had 2-fold higher risk of insulin resistance than those not having it. Despite unfavourable metabolic profile, these patients had low CVD risk.

Keywords: HIV, antiretroviral therapy, ART-associated lipodystrophy, insulin resistance, metabolic syndrome, CVD risk

Original Research – Metabolic Bone Disease

Prevalent Fractures Occur at Relatively Younger Age and Higher Bone Mineral Density among Adult Filipino Men

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Introduction. Osteoporosis in men is markedly underdiagnosed and undertreated even the morbidity and mortality rates with fragility fractures are higher in men. Data are lacking among Asian males. The study identified predictors of osteoporosis and prevalent fractures among adult Filipino men.

Methodology. Records review of Filipino men with age >50 years old screened for bone mineral density (BMD) from 2007 to 2012 was performed. Age, weight, body mass index (BMI), Osteoporosis Self-Assessment Tool for Asians (OSTA) score, smoking status, family history of fracture, diabetes mellitus, physical inactivity and T-score were

considered. Test of proportions, logistic regression analysis, Hosmer-Lemeshow and Wald test were used.

Results. Of the 184 patients, 40.2 and 29.9% have osteopenia and osteoporosis. Sixteen and eighteen osteopenic and osteoporotic men have fragility hip, spine and forearm fractures. Men with age 50 to 69 years have the same risk of osteoporosis and fractures as those with age >70 years. While hip fractures are significantly higher in osteoporotic men ($p<0.05$), vertebral fractures are increased in both osteopenic and osteoporotic men. Even the mere presence of osteopenia predicts the presence of prevalent fractures ($p<0.05$). A high risk OSTA can predict fracture ($p<0.05$). A BMI <21 kg/m2 and current smoking ($p<0.05$) are associated with increased risk of osteoporosis.

Conclusions. Fractures may occur in men <70 years old even at higher BMD. A low BMI and high OSTA are consistent risk factors while smoking may be an emerging risk factor of osteoporosis. The threshold for screening and treatment must be lowered in men contrary to the usual knowledge and practice.

Keywords: osteoporosis, fractures

Original Research – Obesity and Metabolic Syndrome

Body Mass Index, Waist Circumference and Waist-To-Hip Ratio Cut-Off Levels for Overweight and Obesity Predicting Cardiometabolic Diseases among Adult Filipinos in a Rural Community

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Introduction. The risk of developing cardiometabolic diseases (CMD) associated with overweight and obesity among Asians has been found to be increased even at lower body mass index compared to Caucasians matched for age and sex. But due to ethnic differences among different Asian races, adapting a universal cut-off as recommended by the World Health Organization seems to be inappropriate. The objective of the study is to recommend cut-off levels for body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) that will define overweight, obesity and central obesity that would predict CMDs among adult Filipino rural community dwellers aged 18 years old and above.

Methodology. This is a community-based cross-sectional observational study. The study utilized data from Phase II of Diabetes Self-Management Education (DSME) Program conducted by the Diabetes Study Group of the Section of Endocrinology, Diabetes and Metabolism of the University of the Philippines Manila in San Juan, Batangas, Philippines, which determined the prevalence of prediabetes, type 2 diabetes, hypertension, dyslipidemia and metabolic syndrome. It included 332 Filipino adults with no known illnesses, non-pregnant, and residing for at least 6 months in the rural communities of San Juan, Batangas. Weight, height, waist and hip circumferences were measured. Presence of hypertension, type 2 diabetes mellitus and dyslipidemia were determined through blood pressure determination, fasting blood sugar and 2 hours post-75 grams oral glucose tolerance test, and lipid profile respectively. Optimal cut-offs was determined by the intersection of sensitivity and specificity curves of having at least 1 CMD. Area under the receiver operating characteristic (ROC) curve (AUC) will be used to determine the predictive value of BMI, WC and WHR for each CMDs and having at least 1 CMD.

Results. The optimal cut-off for overweight or obesity in males and females relative to occurrence of at least one CMD is a BMI of 22 and 23 kg/m2 respectively. The optimal cut-off for central obesity in males and females relative to occurrence of at least one CMD is a WC of 79 and 77 cm, and a WHR 0.90 and 0.85 respectively. The area under the ROC curve for detecting at least one CMD was largest for BMI among males (0.665, 95% CI 0.516 – 0.813), and WC among females (0.571, 95% CI 0.481 – 0.662).

Conclusions. Similar to findings of other countries in the Southeast Asian region, cut-off levels defining overweight or obesity, and central obesity using BMI, WC and WHR is lower than the currently recommended cut-offs by the WHO among Filipino adults in rural communities, particularly for WC in both sexes, and WHR in males.

Keywords: body mass index, waist circumference, waist-to-hip ratio, obesity

Original Research – Obesity and Metabolic Syndrome

Screening of Anti-Immunosuppressive Activity of *Phyllanthus Amarus Schum. & Thonn.* (Euphorbiaceae) Leaf and Stem Extract on Methylprednisolone-Induced Balb/C Mice

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Introduction. *Phyllanthus amarus* is a herb well known for its medicinal properties and is widely used worldwide. The present study was conducted to evaluate the anti-immunosuppressive activity of ethanolic leaf and stem extract of *P. amarus*.

Methodology. Cholesterol and glucose serum levels, leucocyte count and splenic histology serve as markers of reversible immunosuppression on methylprednisolone-induced Balb/C mice. Twelve mice were divided into 4 groups of 3 mice each. Group I: Mice were injected with 15mg/kg of BW of methylprednisolone (MEP) hemisuccinate intraperitoneally in a single dose (Day 0). Group II: Mice were intraperitoneally injected with a single dose injection of 0.9% NaCl (Day 0). Group III: *Phyllantus amarus* leaf extract was intraperitoneally injected at Day 2, 5, and 8 of the experiment along with 15mg/kg of BW of methylprednisolone hemisuccinate single dose at Day 0. Group IV: *Phyllantus amarus* stem extract, same as in Group III.

Results. In terms of percentage weight gain, methylprednisolone-induced mice treated with leaf and stem extracts registered results comparable with the MEP-treated group. Results of the glucose serum and cholesterol serum levels also revealed no significant effects. The number of leucocytes was significantly reduced ($p<0.05$) by treatment with methylprednisolone but when immunocompromised mice were treated with leaf and stem extracts, the number of leucocytes did not significantly differ from the initial count obtained at day 0. The red pulp width was significantly reduced ($p<0.05$) by MEP-treatment but after treatment with the extracts, the width of the red pulp was increased to measurements comparable with the negative control.

Conclusions. The present study demonstrated that the PaLE and PaSE, at 1 mg/kg concentration, conceivably can reverse the immunosuppression induced by methylprednisolone. In terms of the body weight of the experimental animals, treatments with PaLE and PaSE registered a significantly lower weight gain percentage compared to the NSS-treated group. However, the effect of the extract on body weight is comparable with the MEP-treated group. In terms of glucose serum and cholesterol serum levels, no significant changes were noted among treatments.

Keywords: glucocorticoids, immunomodulation, glucose, cholesterol

Original Research – Others

Thyroid Hormone Activity of Polybrominated Diphenyl Ethers (PBDEs) In Vitro and In Vivo

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Introduction. There have been many concerns regarding the possible adverse effects of thyroid hormone (TH) disrupting chemicals in the environment. Much attention has been paid to brominated flame retardants including polybrominated diphenyl ethers (PBDEs). To understand their hormonal activities, PBDEs and their metabolites were subjected to a TH receptor (TR) binding assay and luciferase reporter gene assays. The in vivo effects were also examined.

Methodology. TR binding affinities of chemicals were determined by the competitive binding assay with rTRa-LBD. To examine the TR dependent transcription activities, MtT/E-2 and CHO cells transiently transfected with a TRE-luciferase reporter were employed. PBDEs were given (i.p.) to neonatal F344 rats. After 24 hours, the mRNA levels of the hepatic TH responsive genes were determined by Q-RT-PCR.

Results. Many of the examined PBDEs exhibited significant affinities to TR. 4'OH-BDE-17 and 2'OH-BDE-28 acted as agonists in the reporter gene assay in MtT/E-2 cells, while they were antagonists in CHO cells. 4-OH-BDE-90, on the other hand, did not show any agonistic activity despite of its high affinity to TR. In neonatal rats, OH-BDEs were capable of inducing hepatic TH responsive gene expression at higher dosages.

Conclusions. Some of the PBDEs, especially the hydroxylated metabolites, were indeed TH-like chemicals. Our results suggested that the activities of PBDEs may differ among target tissues or species; they may act as 'partial' agonists/ antagonists. PBDEs were capable of inducing some of the hepatic TH responsive genes in vivo, albeit requiring the higher doses.

Keywords: endocrine disruptors, thyroid hormones, PBDE, cell type-specific

Original Research – Others

Effect of Prolonged Exhaustive Exercise to Blood Lymphocyte Count and Diameter of Splenic White Pulp

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Introduction. Exercise causes oxidative stress on the immune system. The aim of this study was to examine the effect of prolonged exhaustive exercise to blood lymphocyte count and the diameter of splenic white pulp.

Methodology. Twenty eight male rats (Rattus norvegicus) of Wistar strain were divided into four groups: the control group of fifteen days (K1), the treatment group of fifteen days (P1), the control group of thirty days (K2) and the treatment group of thirty days (P2). Treatment was given as exhaustive swimming with six percent of body weight load on their tail. After treatment, the blood was collected to examine malondialdehyde (MDA) level in serum, and blood lymphocyte count. The animal was then sacrified with decapitation method followed by removal of the spleen and histologic preparation (haematoxylin-eosin staining). The diameter of splenic white pulp was measured by light microscope at 100x magnification. The data were analyzed using one way ANOVA (α=0,05).

Results. The results show that the treatment caused oxidative stress based on blood MDA level. The treatment for fifteen days decreased the diameter of the splenic white pulp, but blood lymphocyte count was still within the normal range. The treatment for thirty days increased the diameter of the splenic white pulp (no significant difference with the control group) and also increased blood lymphocyte count.

Conclusions. Prolonged exhaustive exercise could modulate the immune system based on blood lymphocyte count and diameter of splenic white pulp.

Keywords: malondialdehyde, lymphocytes, splenic white pulp

Clinical Trial – Prediabetes/Diabetes Mellitus

Effects of Sweet Potato Green Leaves on the Glycemic Response of Diabetics

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Introduction. There are epidemiological studies that suggest a strong inverse association between incidence of chronic diseases like diabetes mellitus and intake of plant foods, possibly due to their high nutrient density, complex carbohydrates and low fat contents. The study was conducted to determine the effects of sweet potato green leaves (Ipomea Batatas) on the glycemic responses of diabetics.

Methodology. This is a quasi experimental trial of 23 subjects with diabetes mellitus type 2 who signed the waiver of consent reviewed and approved by the Ethics Review Board of San Pedro Hospital Incorporated, Davao City. Demographic and dietary profiles were determined through interview and 7-day food record. Subjects were asked not to take their medications and supplements and fast for 8-10 hours the night before the blood extraction. Blood glucose response was determined through a venipuncture at 0,30, 60, 90 and 120 minutes after consumption of 50 grams available carbohydrates from the test meals (T1- white bread, T2- white bread and sweet potato green leaves,T3 – white rice and T4 – white rice and sweet potato green leaves). Data were analyzed using descriptive statistics and independent t-test.

Results. Mean blood glucose was 7.68 mmol/L, peak rise happened 60 minutes after consumption of all treatments. Treatment 1 and 2 exhibited glycemic response shortly after 30 minutes, with Treatment 1 higher (65.94; SD-35.40) compared to Treatment 2 (31.45; SD-31.08) with a mean difference of 34.49 (t=3.93), hence highly significant (P<.01). An increase in blood glucose 30 minutes after ingestion of treatment 3 and Treatment 4 was noted, peak rise happened after 60 minutes with mean of 234.73 (SD-51.16) in Treatment 3 and 177.92 (SD-47.94) for treatment 4. Difference in the glycemic responses of Treatment 3 and 4 showed high significance (P<.05). Expected decline of blood glucose levels happened after 90 to 120 minutes for all the 4 treatments.

Conclusions. Sweet potato green leaves when consumed with either bread or rice slow down glycemic responses. Therefore, it can delay glycemic response after a meal. Promotion on the benefits of sweet potato green leaves either as a dish, or part of a dish, or as a fortificant of a processed food product will greatly help the Filipinos and other Asians who are at-risk, in discovering another way of controlling the prevalence of diabetes mellitus.

Keywords: glycemic response, diabetes mellitus

Clinical Trial – Prediabetes/Diabetes Mellitus

A Randomized Controlled Trial on the Efficacy and Safety of Ospital Ng Makati Insulin Infusion Protocol Versus the Texas Insulin Infusion Protocol on Glycemic Control among Adult Non-Surgical Patients Admitted at a Tertiary Hospital

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Introduction. Good glycemic control through the use of insulin infusion therapy (IIT) greatly reduces morbidity and mortality among admitted patients. The purpose of this study is to compare the efficacy and safety of the proposed Ospital ng Makati (OSMAK) Insulin Infusion Protocol (IIP) with an international standard (Texas Insulin Infusion Protocol) on glycemic control of admitted adult non-surgical patients.

Methodology. This is a single-blinded randomized controlled trial conducted among adult non-surgical patients with hyperglycemia admitted at Ospital ng Makati (OSMAK), Philippines. 35 patients were included and randomly assigned to OSMAK IIP (experimental n=20) or Texas IIP (control n=10).

Results. In terms of efficacy, mean CBG was determined for both groups in 3 different periods: during IIT, upon termination of IIT and after IIT up to the last hospital day which all showed significant difference between the two groups as proven by all p values<0.05. Target glucose levels used were based on the recommendations of ADA/AACE for critically ill patients (140-180 mg/dL) and the NICE-SUGAR study (< 180 mg/dL). Both groups did not meet the ideal glucose levels during IIT (p value = 0.01). Upon termination of IIT, the mean CBG in OSMAK IIP was significantly higher (171.68 ± 66.62) but still within the target glucose levels; while in Texas IIP, the mean CBG (84.50 ± 22.04) met the blood glucose target for NICE-SUGAR study but did not meet the ADA/AACE recommendation. Mean CBG after IIT up to the last hospital day was maintained within recommended levels for both treatment groups (169.78 ± 29.16; 147.08 ± 34.90, p value = 0.05). However, both CBG levels recorded in this study were not able to show association with patients' hospital outcome (either discharge or mortality) (p value > 0.05). There was no statistical difference between the two groups in terms of nosocomial infection, number of days requiring mechanical ventilator, number of days on vasopressors, number of ICU days, number of hospital days and mortality. In terms of safety, episodes of hypokalemia and hypoglycemia were noted for both treatment groups but were not statistically significant (p value=0.63; 1.00 respectively).

Conclusions. In reference to an international standard (Texas IIP), OSMAK IIP shows trending towards a safe and effective means of maintaining blood glucose targets among admitted adult non-surgical patients.

Keywords: insulin infusion therapy, glycemic control, insulin infusion protocol, hyperglycemia, insulin infusion pumps

Clinical Trial – Prediabetes/Diabetes Mellitus

Safety and Efficacy of Glaritus® Versus Lantus® in Indian Patients with Type 1 Diabetes Mellitus

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Introduction. Combination therapy with rapid-acting insulin analogues like lispro and long acting insulin analogues such as insulin glargine achieves consistent glycemic control for a longer period of time and is mainstay for management of patients with Type 1 Diabetes Mellitus (T1DM). We compared the safety and efficacy of insulin glargine; Glaritus® (insulin glargine, Wockhardt) with Lantus® (insulin glargine, Sanofi Aventis) in combination with meal time bolus of rapid acting insulin analogue insulin lispro.

Methodology. This was a prospective, randomized (1:1), multicenter (14 study centers across India), comparative, non-inferiority, open-label, parallel group study. Patients (18- 55 yr) diagnosed with T1DM and on insulin regimen ≥12 months were included. After screening and run-in period (4 wks), patients received either Glaritus® or Lantus® for 12 wks.

Results. Of 171 randomized patients (Glaritus® arm- 86 subjects; Lantus® arm-85 subjects), 161 completed the study. The baseline characteristics were well-matched. The mean reduction in HbA1c from baseline to Wk 12 was comparable with Glaritus® (0.69±1.81) and Lantus® (-0.53 ±1.94; p=0.454); difference of adjusted means of change in HbA1c was 0.20 (<USFDA specified non-inferiority margin of 0.4) suggesting non-inferiority of Glaritus®. The mean immunogenic response was comparable in Glaritus® and Lantus® arm, 0.25±0.97 and 0.02±0.68, respectively (p=0.306). Similar number of patients in Glaritus® (n=22, 27.2%) and Lantus® (n=22, 28.6%) arm had episodes of hypoglycemia. Overall, 24 adverse events (14%, all mild to moderate) were reported, 14 in Lantus® and 10 in Glaritus® arm.

Conclusions. Glaritus® is safe, effective, and comparable to Lantus®

Keywords: diabetes mellitus, Insulin Glargine, Insulin Lispro, blood glucose

Original Research – Prediabetes/Diabetes Mellitus

Prevalence, Clinical Profile, and Glycemic Variability of Celiac Disease in Patients with Type 1 Diabetes Mellitus in Western Uttar Pradesh, India

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Introduction. Celiac disease is frequently associated with type 1 diabetes mellitus, but is usually ill-defined and not usually suspected until the disease become advance. This study aimed to determine the prevalence, clinical profile and glycemic variability and the effect of gluten free diet on growth and diabetic control in celiac type 1 diabetes patients in a tertiary care referral centre in western Uttar Pradesh, India.

Methodology. A total of two hundred and fifty six patients were screened (149 males and 107 females) during the study period of two years, patients were evaluated for the clinical signs, biochemical investigations and family history of celiac disease in tertiary care health center in western Uttar Pradesh.

Results. Twenty four (9.37%) patients were diagnosed to have celiac disease; the mean age at diagnosis of diabetes was 9.34 ± 7.3 years. Only 1/24 patients with celiac disease had been diagnosed before detection of diabetes mellitus. The common manifestations were normocytic normochromic anemia (66.6%) followed by diarrhoea (62.5%), abdominal pain/bloating sensation (58.3%), and short stature (58.3%). Weight SDS increased from –0.12+1.3 at the start of gluten free diet to 0.8+0.9 after 12 months later ($p<0.05$). Height SDS increased from –2.46+1.1 at the start of gluten free diet to –2.14+0.9 after 12 months later ($p=0.087$). Bone age SDS increased from 9.2+6.3 at the start of gluten free diet to 10.3+6.7 after 12 months later. Height velocity increased from 4.7+0.7 cm/year in the year before treatment to 5.1+1.2during treatment ($p= 0.05$). The increased in Hemoglobin, serum calcium, and serum iron is statistically significant ($p<0.05$).

Conclusions. Celiac disease was found to be significantly associated with type 1 diabetes, timely identification of these disorder are of paramount important for better glycemic control and to reduced the morbidity and mortality associated with the conditions.

Keywords: celiac disease, diabetes mellitus, uncontrolled hyperglycemia