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The 4th International Congress on

Abdominal Obesity

Bridging the Gap Between Cardiology and Diabetology

Abstract Book

Seoul, Korea

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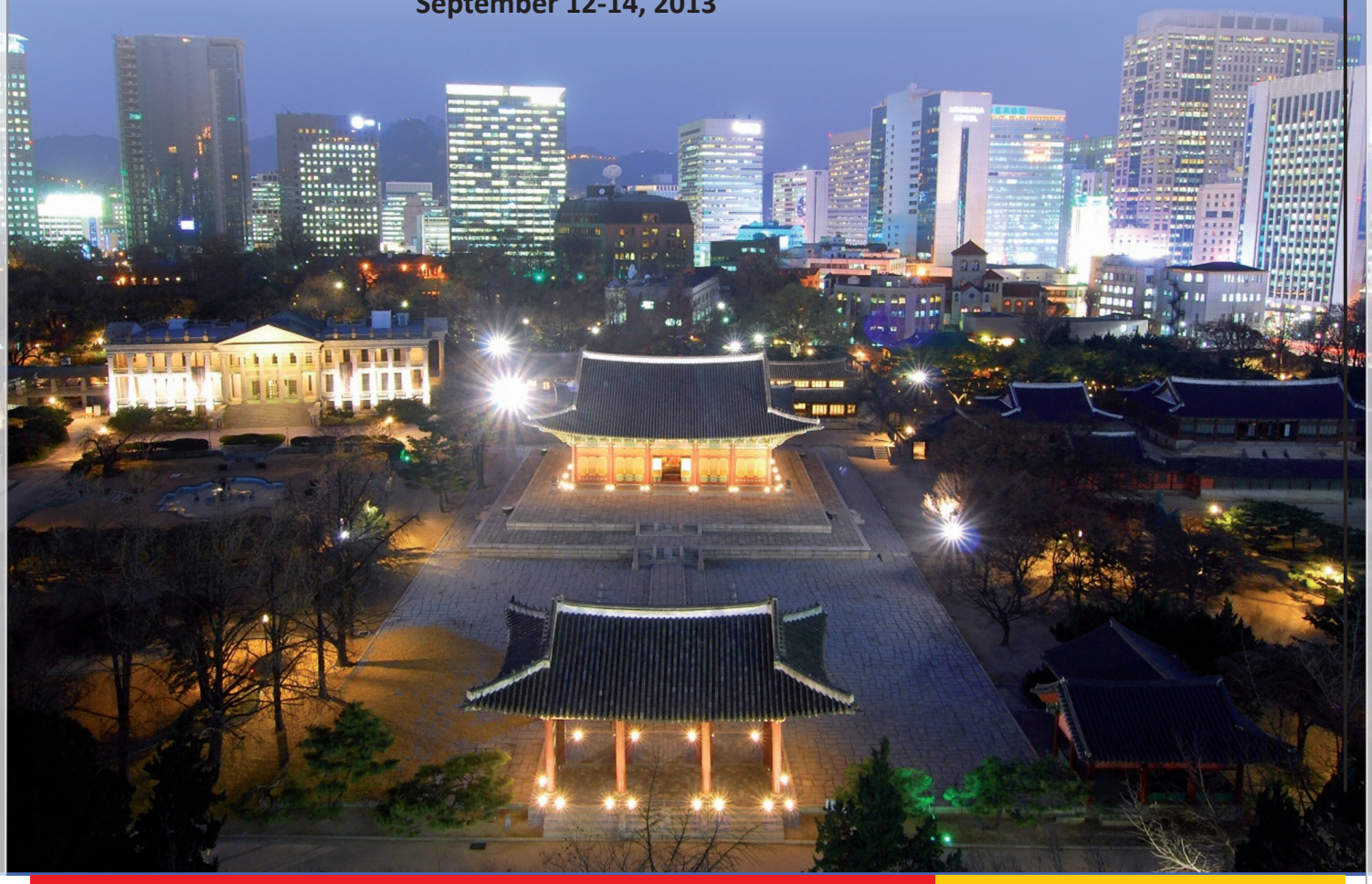

International Chair on Cardiometabolic Risk

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UNIVERSITÉ LAVAL

CENTRE DE RECHERCHE INSTITUT UNIVERSITAIRE DE CARDIOLOGIE ET DE PNEUMOLOGIE DE QUÉBEC

Table of Contents

Welcome Letter

Dear Colleagues,

We would like to welcome you to the 4th edition of the "International Congress on Abdominal Obesity: Bridging the Gap Between Cardiology and Diabetology" (ICAO). This meeting is organized jointly by the International Chair on Cardiometabolic Risk and the Korean Society of Lipidology and Atherosclerosis. The meeting will take a multidisciplinary approach to the assessment and management of abdominal obesity as a key risk factor for the development of diabetes and cardiovascular disease.

Evidence suggests that the worldwide epidemic of abdominal obesity cannot be handled by the current medical model in which complications such as hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease are often evaluated and managed in isolation. Medical treatment focuses on the management of complications by pharmacotherapy and expensive procedures rather than on working upstream in order to avoid the development of abdominal obesity and related complications. In addition, physicians most often do not have access to the proper multidisciplinary resources to improve patients' nutritional and physical activity habits and to prevent the development of these costly cardiometabolic diseases.

The biological and environmental causes of abdominal obesity will be examined at this meeting. We will highlight emerging concepts with a focus on translation to define new paradigms for its assessment and management. The Congress will examine and discuss novel approaches, and share scientific and clinical data to benefit regional healthcare professionals, clinicians and scientists. The fight against the worldwide epidemic of abdominal obesity, diabetes, and cardiovascular disease represents a monumental clinical and public health challenge. The ICAO represents one important scientific platform to address this issue for the benefit of patients and health professionals.

Some of the key topics to be addressed include:

- Abdominal obesity in Asia;
- Pathophysiology of abdominal obesity and related cardiometabolic risk;
- Abdominal obesity in cardiology/CVD risk;
- Cardiometabolic risk: From basic to translational aspects;
- Assessment of abdominal obesity and global cardiometabolic risk;
- Management of abdominal obesity and global cardiometabolic risk: Physical activity/exercise, nutrition, global management.

We are very happy to welcome you in Seoul for this exciting international scientific event that will tackle these important and growing worldwide health problems.

Sincerely yours,

Jean-Claude Coubard
Congress Chairman of ICCR

Jean-Pierre Després
Congress Chairman of ICCR

Jong Ho Lee
President of KSLA

Chee Jeong Kim
Chief Director of KSLA

About the International Chair on Cardiometabolic Risk

The International Chair on Cardiometabolic Risk is an independent, academic, multidisciplinary organization affiliated with Université Laval and located at Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec in Québec City, Canada. It is composed of an Executive Council and a Scientific Council.

The members of both councils have been chosen based on their expertise, their remarkable scientific contributions and their status as world leaders in their discipline. The makeup of both councils exemplifies the multidisciplinary nature of the Chair, with all members active in complementary areas of expertise. The Chair provides a forum for them to share their knowledge and expertise regarding diverse pathophysiological conditions eventually leading to cardiovascular disease.

A key aspect of the Chair is its international and multidisciplinary character, with the following disciplines represented: cardiology, diabetology, lipidology, endocrinology and metabolism, obesity, nutrition, physical activity and basic research.

The Chair organizes and participates in an array of activities at international medical congresses while reaching out to both scientific and lay communities. The Chair's website, which was launched in the fall of 2007, is a key component of its mission. The website is the most comprehensive, up-to-date and easy-to-use source of information on abdominal obesity and cardiometabolic risk. Intended for both health professionals and the general public, it uses state-of-the-art technology to help visitors better understand the risk factors and markers that must be addressed and the lifestyle changes that must be made in order to prevent abdominal obesity, type 2 diabetes and cardiovascular disease.

The Chair's website is highly interactive and features free slides, webcasts, and videos in which world-renowned experts discuss themes relevant to abdominal obesity and cardiometabolic risk. The Chair also publishes the **CMReJournal**, which is available through its website. The e-journal complements the Chair's website and provides up-to-date information on abdominal obesity and related cardiometabolic risk for a range of audiences. Also available on the website is a downloadable iPad application that allows physicians and health professionals to access their patients' cardiometabolic risk through a comprehensive set of algorithms. Moreover, algorithms are included to access level of physical activity and nutritional quality, two key correlates of cardiometabolic health.

By providing a platform for integrated research, developing physician and patient education programs and working to create new prevention and treatment strategies, the Chair is committed to stopping and reversing the abdominal obesity pandemic for the benefit of patients and society alike.

Our website can be found at: **www.myhealthywaist.org**

Posters

Abdominal Obesity / Body Fat Distribution

ICAO2013-037
REAPPRAISAL OF WAIST CIRCUMFERENCE CUTOFF VALUES FOR CENTRAL OBESITY ACCORDING TO OBESITY

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Objective The aim of this study was to redefine waist circumference cutoff values for central obesity to predict atherosclerosis according to obesity.

Methods A total 4753 subjects (non-diabetes 1063, diabetes 3690), aged over 18 years, were recruited from the local community, Seoul and Seongnam, Korea. Atherosclerosis was defined as 1) history of coronary artery disease or cerebrovascular disease or 2) presence of plaque in carotid artery or 3) thickened carotid artery intima-media thickness greater than 1 SD compared with age & sex matched mean value. Obesity was defined as a body mass index ≥ 25 kg/m^2. The insulin sensitivity index (Kitt) was derived by a short insulin tolerance test in diabetic subjects.

Results The optimal waist circumference as obtained from receiver operating characteristic curve for identifying atherosclerosis in non-diabetic subjects was 77.25 cm in non-obese women, 85.75 cm in obese women, 84.75 cm in non-obese men, and 92.90 cm in obese men, respectively. These cutoff values displayed the maximal Youden's index compared with conventional cutoff values (> 90 cm for men and > 80 cm for women) (0.205 vs 0.142 in non-obese women, 0.250 vs 0.056 in obese women, 0.252 vs 0.065 in non-obese men, and 0.126 vs 0.066 in obese men, respectively). When applying the optimal cutoff values in diabetic subjects, Kitt of the intermediate groups created by applying both conventional and optimal cutoff values was closed to central obese group in non-obese patients and to non-central obese group in obese patients. Thus, our optimal cutoff values were also meaningful in diabetic subjects.

Conclusion In conclusion, the conventional cutoff value of waist circumference for central obesity was overestimated in non-obese people and underestimated in obese people. Thus, it is necessary to redefine waist circumference cutoff values for central obesity according to obesity.

Table 3. Comparison of waist circumference cutoff values for central obesity to predict atherosclerosis according to obesity in non-diabetic subjects

		Cutoff (cm)	Sensitivity (%)	Specificity (%)	Youden's index
Non-obese	Men	84.75	57.6	67.6	0.252
		90	13.0	93.5	0.065
	Women	77.25	67.7	52.8	0.205
		80	48.5	65.7	0.142
Obese	Men	92.9	49.2	63.4	0.126
		90	71.0	35.6	0.066
	Women	85.75	80.3	44.7	0.250
		80	99.0	6.6	0.056

Table 4. Comparison of the insulin resistance (Kitt) according to sex and obesity adjusted for age, diabetes duration and drug usage.

Men	Non-obese			Obese		
WC (cm)	< 84.75[a]	84.75 – 90[b]	> 90[c]	< 90[a]	90 – 92.9[b]	> 92.9[c]
N	839	348	57	397	112	362
K_{ITT} (%/min)	2.27 ± 1.03	1.90 ± 0.88*	1.69 ± 0.70*	2.07 ± 0.97	1.93 ± 0.83	1.67 ± 0.77*†
Women	Non-obese			Obese		
WC (cm)	< 77.25[a]	77.25 – 80[b]	> 80[c]	< 80[a]	80 – 85.75[b]	> 85.75[c]
N	576	174	221	67	174	363
K_{ITT} (%/min)	2.30 ± 1.02	2.00 ± 0.90*	1.84 ± 0.88*	2.17 ± 0.88	2.00 ± 0.86	1.75 ± 0.85*†

a: non-central obese group, b: intermediate group, c: central obese group
K_{ITT}: insulin sensitivity index
WC: waist circumference
*P<0.05 vs. a
†P<0.05 vs. b

ICAO2013-054

OBSERVATION OF ABDOMINAL FAT MASS AFTER SPINE FUSION WITH BONE MORPHOGENETIC PROTEINS-2 IN OVARIECTOMIZED RAT

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Objective Accumulations of excessive fat in abdominal compartments are related with cardiovascular disease, type 2 diabetes, and obesity. We investigated the change of abdominal fat mass after spine fusion with bone morphogenetic proteins-2 in ovariectomized rat.

Methods Female SD rats (7 weeks old) were ovariectomized to induce osteoporosis. After 6 weeks, ovariectomized rats were divided two groups as following: one group was given a sham operation and other group underwent with spine fusion with bone morphogenetic proteins-2. In this study, we examined the amount of food intake, weight gain, food efficiency ratio, levels of serum biochemical lipid-related biomarkers in blood for 6 weeks after spine fusion. Additionally, we observed the pathologic changes with hematoxylin & eosin from extracted organs, abdominal fat mass and bone mass in fusion location between L4 and L5. The measurement of adipose tissue and bone mineral density in experimental animals was quantified with micro-computed tomography (CT) and dual energy X-ray absorptiometer (DEXA) at a 6 weeks after spine fusion.

Results The rat treated bone morphogenetic proteins-2 gained the weight and increased in the serum level of triglycerides, compared to sham mice group. In addition, abdominal fat volume evaluated by CT in bone morphogenetic proteins-2-treated groups was increased compared to fat volume on sham group.

Conclusion These results suggest that spine fusion with bone morphogenetic proteins-2 in ovariectomized rat increase body weight and abdominal fat mass, although increasing bone mineral density.

ICAO2013-092

EPICARDIAL ADIPOSE TISSUE: RELATIONSHIP BETWEEN MEASUREMENT LOCATION AND METABOLIC SYNDROME

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Objective Epicardial adipose tissue (EAT) is a contributing factor of metabolic syndrome (MS) and coronary artery disease (CAD). However, it is still unclear which measurement location of EAT area best reflects its metabolic risk and total EAT volume. The purpose of our study was to investigate the distribution of EAT and its relationship to the total EAT volume and MS.

Methods To assess volume and cross-sectional areas of EAT, coronary CT angiography images were obtained in 256 asymptomatic subjects. The EAT areas within the threshold range of -190 to -30 Hounsfield units (HU) were measured at six representative slices.

Results Correlations between single slice EAT areas and total EAT volumes were generally high across all measurement locations (correlation coefficient $r > 0.80$). EAT areas across all measurement locations were significantly increased linearly with increasing number of MS components. EAT areas were significantly associated with MS at all measurement locations after adjusting for age, smoking, alcohol and BMI. The highest odds ratio (OR) between EAT area and metabolic syndrome was at the LMCA level after adjustment for smoking, alcohol and BMI (OR 5.86; 95% CI 3.47-9.90; $p < 0.001$). The OR between EAT area and CAC was also significant in LMCA locations (OR 1.56; CI 1.01-2.39; $p = 0.042$).

Conclusion We demonstrated that the single-slice EAT area measurement is a simple and reliable method compared with time-consuming volumetric measurements. The EAT area at the LMCA level was the best single slice representing the risk of metabolic syndrome and coronary atherosclerosis.

ICAO2013-099
NO ETHNIC DIFFERENCES IN TRUNK OR LEG FAT MASS IN PREMENOPAUSAL OVERWEIGHT WOMEN

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Objective Body composition and body fat distribution differs across ethnicity. It is reported that Asian have a higher percentage body fat and greater trunk fat compared with Caucasian (Ca) and African-American (AA) for the same BMI. Body fat distribution is associated with increased risk of chronic disease. This study investigated in overweight premenopausal women: 1) whether differences exist in fat distribution in Korean compared to Ca and AA, and 2) the independent associations between trunk fat and cardiovascular risk factors.

Methods We examined differences in fat percent and body fat distribution among overweight (BMI>25 kg/m^2) premenopausal women, Ca (n=24), AA (n=32) living in New York and Korean (Kr, n=49) living in Seoul. Weight, height and the percentage of body fat (PBF) by dual energy X-ray absorptiometry (DXA) were measured. DXA quality control was preformed between both sites. Fasting serum measures of glucose, total cholesterol, HDL cholesterol, and triglycerides were acquired. General linear models were used to identify the independent effects of trunk fat on each risk factor after covarying for total fat, age, ethnicity and 2-way interactions.

Results Kr women had smaller leg fat mass and greater trunk fat mass compared to Ca and AA ($p<0.05$). After adjusting for age, height and total fat mass, these differences were no longer statistically significant. A significant positive association was found between trunk fat and glucose ($p<0.05$) that was similar across ethnic groups.

Conclusion There are no ethnic differences in trunk fat mass and leg fat mass after adjusting for age, height and total fat mass in overweight premenopausal women. The association between trunk fat and glucose was not influenced by ethnicity.

ICAO2013-127

COMPARISON OF ANTHROPOMETRIC INDICES AS A PREDICTOR OF HYPERTENSION IN KOREAN POPULATION: KOREAN GENOME AND EPIDEMIOLOGY STUDY

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Objective Obesity is one of the most significant risk factors for hypertension. However, there is still controversy regarding which measure is the best predictor for hypertension risk. We compared body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) of subjects as a predictive indicator for development of hypertension.

Methods The data were obtained from The Korean Genome and Epidemiology Study which is a large-population prospective cohort study. There were 4,454 subjects (men=2,218, women=2,326) aged 40-69, who did not have hypertension at baseline study included in this study. Receiver operating characteristic (ROC) analysis was used to compare discrimination abilities and determine optimal cut-off values.

Results During 4-year follow-up, the cumulative incidence of hypertension was 18.05% in men and 16.08% in women. The incidence rate of hypertension significantly increased with increment of anthropometric indices in both sexes. The area under the ROC curve (AUC) of BMI was smaller than the central obesity indices in both sexes (Table1).
The ROC curves of WC, WHR and WHtR were significantly different (p<0.01) compared with BMI. The optimal cut-off values for predicting hypertension by using Youden index were 23.59 kg/m^2, 83.33 cm, 0.88 and 0.49 in men and 25.63 kg/m^2, 80.37 cm, 0.86 and 0.51 in women for BMI, WC, WHR and WHtR, respectively.
Table 2 shows the odds ratios (ORs) for incident hypertension according to the obesity status by anthropometric indices. After adjusting with age, smoking status, drink consumption, family history of hypertension and diabetes, anthropometric indices were significantly related to incident hypertension during follow-up period. In both sexes, the OR of BMI for hypertension incidence was lower than other anthropometric indices related with the central obesity.

Conclusion Central obesity indices were better than BMI in the prediction of hypertension for Korean people. WHtR can be recommended as a useful screening tool for the prediction of hypertension with respect to the following strengths. First, WHtR is simple and consumer-friendly because it's cut-off values is 0.5 regardless of difference of sex, ethnicity and age. Second, WHtR is possible to be converted public message for adult "to keep your WC below your half height" in prevention of hypertension.

Table 1. The area under the ROC curve (AUC) and cut-off points for anthropometric indices to predict the hypertension

Anthropometric Index	AUC (95% CI)	Cut-off point	Sensitivity (%)	Specificity (%)	Youden's index indexin	+PV	-PV
Men							
BMI (kg/m^2)	0.58 (0.56~0.60)	23.59	66.15	47.42	0.14	21.70	86.41
WC (cm)	0.62 (0.60~0.64) ***	83.33	59.90	57.91	0.18	23.87	86.77
WHR	0.62 (0.60~0.64) **	0.88	67.97	49.66	0.18	22.92	87.56
WHtR	0.62 (0.60~0.64) ***	0.49	69.27	48.91	0.18	23.00	87.84
Women							
BMI (kg/m^2)	0.57(0.55~0.59)	25.63	42.78	71.21	0.14	22.16	86.66
WC (cm)	0.66(0.64~0.68) ***	80.37	66.04	60.45	0.26	24.24	90.28
WHR	0.68(0.66~0.70) ***	0.86	71.12	57.94	0.29	24.47	91.28
WHtR	0.68(0.66~0.70) ***	0.51	75.13	53.18	0.28	23.52	91.78

95% CI, 95% confidence interval; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height-ratio, +PV, positive predictive value;
-PV, negative predictive value; Youden's, Youden index(Sensitivity+Specificity-1).
** *P* <0.01, *** *P* <0.001 *vs* BMI.

Table 2. Association between various anthropometric indices and incident hypertension according to the obesity status

Variables	Men (n=2,128)			Women (n=2,326)		
	Model 1 ORs (95% CI)	Model 2 ORs (95% CI)	Model 3 ORs (95% CI)	Model 1 ORs (95% CI)	Model 2 ORs (95% CI)	Model 3 ORs (95% CI)
BMI ≥ 25 kg/m$^{2a)}$	1.57(1.25~1.97)	1.76(1.40~2.23)	1.76(1.39~2.22)	1.60(1.28~2.00)	1.59(1.26~2.01)	1.60(1.27~2.03)
WC ≥ 90/85 cm$^{b)}$	2.28(1.75~2.98)	2.32(1.77~3.03)	2.33(1.78~3.06)	2.53(2.01~3.17)	1.86(1.47~2.37)	1.89(1.49~2.41)
WHR ≥ 0.9/0.85$^{c)}$	1.90(1.52~2.37)	1.78(1.42~2.24)	1.76(1.40~2.21)	3.50(2.72~4.50)	2.31(1.76~3.03)	2.32(1.77~3.04)
WHtR ≥ 0.5	2.00(1.60~2.50)	1.97(1.57~2.47)	1.98(1.58~2.48)	3.55(2.71~4.65)	2.39(1.79~3.17)	2.37(1.78~3.17)

a) BMI, WHO (2000)
b) WC ≥ 90 cm for men and ≥ 85 cm for women, Korean Society for the Study of Obesity (2007)
c) WHR ≥ 0.9 for men and ≥ 0.85 for women, WHO (1999)

ORs, odds ratios; 95% CI, 95% confidence interval; BMI, body mass index; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio;
WHtR, waist-to-height-ratio.
Model 1, unadjusted. Model 2, adjusted for age. Model 3, adjusted for

ICAO2013-155

WAIST-HEIGHT RATIO AS PREDICTOR FOR CARDIOMETABOLIC RISK IN MEXICAN CHILDREN AND ADOLESCENTS

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Objective To assess whether waist-to-heigth-ratio (WHR) is a better indicator of cardiometabolic risk factors than body mass index (BMI) or body fat.

Methods A cross-sectional study was undertaken with 1417 children and adolescents aged 7 to 19 years old, participants of Mexican Health Worker Cohort Study. WHR, BMI and body fat were measured by trained staff according to standardized procedures, (weight, height and DEXA). Cardiometabolic risk factors (CRF) was defined according IDF criteria. The WHR discriminative ability to predict FRC was assessed using ROC curves.

Results There were significant correlations between WHR with BMI (r=0.68, p<0.001), body fat (r=0.70, p<0.001), SBP (r=0.16, p<0.001), DBP (r=0.19, p<0.001), LDL (r=0.17, p<0.001), HDL (r=-0.22, p<0.001), PCR (r=0.09, p=0.003).
BMI and body fat areas under the curve were similar for all the cardiometabolic factors (0.86 and 0.89, respectively) but the WHR was higher (0.92). A WHR cut-off value of >0.52 had a of sensitivity of 91.3 and specificity of 80.0 for screening metabolic syndrome and classifies correctly to 82%.

Conclusion The WHR was sensitive in screening for metabolic syndrome. The WHR is a useful and simple clinical measure that does not require reference tables to discriminate children and adolescents with cardiometabolic risk.

ICAO2013-156

SLEEP DURATION IS ASSOCIATED WITH OBESITY IN PREMENOPAUSAL WOMEN BUT NOT IN PERIMENOPAUSAL AND POSTMENOPAUSAL WOMEN IN KOREA

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Objective In the present study, we investigated the association between sleep duration and obesity, including both abdominal and general obesity, in the different menopausal status among middle-aged women in Korea.

Methods We conducted a cross-sectional study on 44 to 56 aged Korean women (n=2,201) who visited the Samsung Medical Center for their regular health check-ups in 2012. The study population was divided into three groups according to their menopausal status; premenopause (n=809, 36.8%), perimenopause (n=731, 33.2%), and postmenopause (n=661, 30.0%). The self-reported usual sleep duration per night during the past month was measured by the Pittsburgh Sleep Questionnaire Index (PSQI). The odds ratios (ORs) for abdominal obesity [waist circumference (WC) ≥ 85cm] and general obesity [body mass index (BMI) ≥ 25.0 kg/m^2] were examined according to the sleep duration (categorized as < 6 h, 6-7 h, and ≥ 7 h (reference category)) across the different menopausal status.

Results The prevalence of abdominal and general obesity in the population were 20.8% (n=455) and 23.1% (n=506), respectively. The number of women who slept < 6 h, 6-7 h, and ≥ 7 h was 457 (23.1%), 694 (35.1%), and 826 (41.8%), respectively. Compared to women who slept more than 7 hours per night, premenopausal women who slept 6 to 7 hours or less than 6 hours had significantly greater ORs for both abdominal obesity (OR: 1.92; 95% Confidence Interval [CI]: 1.13-3.24, OR: 2.22; 95% CI: 1.22-4.02) and general obesity (OR: 2.42; 95% CI: 1.45-4.03, OR: 2.48; 95% CI: 1.38-4.46), respectively, controlling for potential confounders. The adjusted ORs (95% CIs) associated with sleeping less than 6 hours (vs. more than 7 hours) were 1.72 (1.02-2.89) for abdominal obesity and 1.81 (1.06-3.07) for general obesity, but after further adjustment for insulin resistance, the association between sleep duration and obesity was not detected in perimenopausal women. No association was observed between sleep duration and abdominal obesity and general obesity in postmenopausal women.

Conclusion Sleep duration < 6 h and both abdominal and general obesity were significantly associated only in premenopausal women among middle-aged women in Korea.

Table 1. Descriptive characteristics of the total sample of middle-aged women and the three subgroups, according to the different sleep duration

	All	< 6h	6-7 h	> 7h	*P-value*[a]
Age	48.84 (3.47)	49.10 (3.56)	48.53 (3.38)	48.97 (3.47)	0.025
Sleep duration (hour)	6.39 (1.11)	N/A	N/A	N/A	N/A
Waist circumference (cm)	78.95 (7.86)	79.98 (8.38)	78.67 (7.89)	78.64 (7.52)	0.011
Abdominal obesity	455 (20.8)	124 (27.3)	138 (19.9)	149 (18.0)	<0.001
BMI (kg/m2)	23.03 (3.06)	23.33 (3.32)	23.02 (3.09)	22.89 (2.89)	0.052
General obesity	506 (23.1)	128 (28.0)	169 (24.5)	159 (19.2)	<0.001
Depressive symptom score[b]	8.72 (8.01)	10.24 (8.92)	7.97 (7.29)	8.53 (7.99)	<0.001
HOMA-IR	1.42 (1.06)	1.53 (1.35)	1.36 (0.91)	1.40 (0.99)	0.254
Marital status	1925 (91.6)	396 (90.4)	636 (92.7)	736 (91.8)	0.533
Education level	1191 (58.1)	242 (55.0)	421 (63.0)	463 (58.9)	0.361
Menopausal status					0.569
Premenopause	809 (36.8)	153 (33.5)	278 (40.1)	311 (37.7)	
Perimenopause	731 (33.2)	170 (37.2)	223 (32.1)	271 (32.8)	
Postmenopause	661 (30.0)	134 (29.3)	193 (27.8)	244 (29.5)	
Job status					0.515
Yes	908 (42.0)	186 (41.2)	333 (48.2)	330 (40.4)	
No	891 (41.2)	206 (45.7)	261 (37.8)	368 (45.1)	
Don't know	365 (16.9)	59 (13.1)	97 (14.0)	118 (14.5)	
Alcohol consumption[b]					0.018
Intervention level-Alcohol education	1988 (90.4)	397 (87.1)	630 (90.9)	752 (91.2)	
Intervention level-Simple advice	157 (7.1)	40 (8.8)	49 (7.1)	55 (6.7)	
Intervention level-Simple advice plus	25 (1.1)	9 (2.0)	7 (1.0)	9 (1.1)	
Intervention level-Referral to specialist	28 (1.3)	10 (2.2)	7 (1.0)	9 (1.1)	
Physical activity[b]					0.466
Low	1185 (54.0)	245 (54.0)	332 (48.0)	457 (55.3)	
Moderate	706 (32.2)	150 (33.0)	247 (35.7)	258 (31.2)	
High	304 (13.8)	59 (13.0)	113 (16.3)	111 (13.4)	
Perceived health					0.837
Good	574 (26.1)	101 (22.1)	202 (29.1)	216 (26.2)	
Fair	1257 (57.1)	267 (58.4)	398 (57.3)	486 (58.8)	
Bad	216 (9.8)	65 (14.2)	48 (6.9)	80 (9.7)	
Don't know	154 (7.0)	24 (5.3)	46 (6.6)	44 (5.3)	

Values are expressed as mean (SD) for continuous variables or N (%) for categorical variables.

[a] *p* values were calculated by chi-squared test (categorical variables), ANOVA (for normally distributed continuous variables), and Kruskal-Wallis test (for non-normally distributed continuous variables).

[b] Depressive symptoms, alcohol consumption, and physical activity levels were measured by the Korean version of the Center for Epidemiologic Studies-Depression Scale (CES-D), Alcohol Use Disorders Identification Test (AUDIT), and International Physical Activity Questionnaire (IPAQ), respectively.

Table 2. Unadjusted and adjusted ORs (95% CI) for abdominal and general obesity according to the different sleep duration in pre-, peri-, post-menopausal period

Abdominal obesity												
	All			Premenopause			Perimenopause			Postmenopause		
	n	OR(95% CI)	*P*	n	OR(95% CI)	*P*	n	OR(95% CI)	*P*	n	OR(95% CI)	*P*
Unadjusted												
≥ 7h (reference)	826	1.00		311	1.00		271	1.00		244	1.00	
6-7 h	692	1.132 (0.875-1.464)	0.346	278	**1.865 (1.203-2.890)**	0.005	221	0.867 (0.544-1.383)	0.550	193	0.865 (0.550-1.362)	0.531
< 6h	455	**1.702 (1.297-2.234)**	<0.001	152	**2.258 (1.377-3.705)**	0.001	169	**1.662 (1.056-2.616)**	0.028	134	1.317 (0.819-2.117)	0.257
Model 1												
≥ 7h	826	1.00		311	1.00		271	1.00		244	1.00	
6-7 h	692	1.151 (0.889-1.490)	0.286	278	**1.876 (1.210-2.910)**	0.005	221	0.879 (0.551-1.403)	0.589	193	0.870 (0.552-1.370)	0.547
< 6h	455	**1.691 (1.287-2.221)**	<0.001	152	**2.266 (1.381-3.718)**	0.001	169	**1.661 (1.054-2.617)**	0.029	134	1.295 (0.804-2.086)	0.287
Model 2												
≥ 7h	698	1.00		259	1.00		229	1.00		210	1.00	
6-7 h	599	1.161 (0.879-1.535)	0.293	237	**1.889 (1.161-3.075)**	0.010	194	0.958 (0.569-1.614)	0.873	168	0.912 (0.561-1.481)	0.709
< 6h	369	**1.653 (1.222-2.234)**	0.001	130	**2.272 (1.312-3.934)**	0.003	134	**1.720 (1.024-2.890)**	0.040	105	1.129 (0.654-1.950)	0.662
Model 3												
≥ 7h	695	1.00		258	1.00		229	1.00		208	1.00	
6-7 h	589	1.143 (0.845-1.547)	0.386	236	**1.915 (1.133-3.238)**	0.015	191	0.957 (0.542-1.691)	0.880	162	0.881 (0.516-1.504)	0.642
< 6h	365	**1.623 (1.170-2.252)**	0.004	130	**2.217 (1.224-4.015)**	0.009	134	1.659 (0.939-2.930)	0.081	101	1.150 (0.631-2.095)	0.648
General obesity												
	All			Premenopause			Perimenopause			Postmenopause		
	n	OR(95% CI)	*P*	N	OR(95% CI)	*P*	N	OR(95% CI)	*P*	N	OR(95% CI)	*P*
Unadjusted												
≥ 7h (reference)	826	1.00		311	1.00		271	1.00		244	1.00	
6-7 h	690	**1.361 (1.065-1.739)**	0.014	278	**2.099 (1.401-3.146)**	<0.001	220	1.105 (0.704-1.735)	0.664	192	1.000 (0.646-1.548)	1.000
< 6h	456	**1.637 (1.253-2.139)**	<0.001	153	**2.212 (1.388-3.525)**	0.001	169	**1.653 (1.047-2.611)**	0.031	134	1.187 (0.739-1.908)	0.478
Model 1												
≥ 7h (reference)	826	1.00		311	1.00		271	1.00		244	1.00	
6-7 h	690	**1.379 (1.079-1.763)**	0.010	278	**2.139 (1.425-3.211)**	<0.001	220	1.128 (0.717-1.775)	0.602	192	0.997 (0.644-1.544)	0.991
< 6h	456	**1.628 (1.245-2.129)**	<0.001	153	**2.233 (1.400-3.563)**	0.001	169	**1.653 (1.045-2.617)**	0.032	134	1.196 (0.743-1.925)	0.460
Model 2												
≥ 7h (reference)	698	1.00		259	1.00		229	1.00		210	1.00	
6-7 h	597	**1.377 (1.053-1.801)**	0.019	237	**2.254 (1.424-3.569)**	0.001	193	1.221 (0.729-2.047)	0.448	167	0.950 (0.595-1.515)	0.828
< 6h	370	**1.578 (1.171-2.127)**	0.003	131	**2.400 (1.422-4.052)**	0.001	134	**1.805 (1.062-3.068)**	0.029	105	0.861 (0.498-1.490)	0.593
Model 3												
≥ 7h (reference)	695	1.00		258	1.00		229	1.00		208	1.00	
6-7 h	587	**1.425 (1.060-1.915)**	0.019	236	**2.421 (1.453-4.033)**	0.001	190	1.302 (0.737-2.298)	0.364	161	0.940 (0.561-1.577)	0.815
< 6h	366	**1.491 (1.071-2.076)**	0.018	131	**2.483 (1.383-4.457)**	0.002	134	1.715 (0.952-3.091)	0.073	101	0.693 (0.370-1.298)	0.252

Model 1 was adjusted for age. Model 2 was further adjusted for the marital status, education attainment, job status, alcohol consumption, physical activity, perceived health, and depression level. The depression level was measured by CES-D. Subjects were categorized as having depression symptoms for 16 or higher score on CES-D. Model 3 was further adjusted for HOMA-IR.

ICAO2013-167

COMPARISON OF ABDOMINAL AND MID-THIGH COMPOSITION IN VISCERALLY OBESE MEN WITH NORMAL, IMPAIRED GLUCOSE TOLERANCE AND T2D: ASSOCIATION WITH IR

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Objective Visceral adiposity and ectopic lipid accumulation in the skeletal muscle have both been shown to be related to cardiometabolic disturbances. However, their respective roles in insulin resistance remain debated. The objectives of the present study were 1) To investigate the distribution of abdominal and mid-thigh composition assessed by computed tomography (CT) in men characterized by either normal glucose tolerance, impaired glucose tolerance and type 2 diabetes and 2) to examine the respective associations with insulin resistance.

Methods Glucose tolerance status was assessed by a 75g oral glucose tolerance test whereas abdominal and mid-thigh composition was determined by CT. Insulin resistance was estimated by the HOMA-IR index in 195 men characterized by normal glucose tolerance (n=71), impaired glucose tolerance (n=98) and type 2 diabetes (n=26).

Results As expected, IGT and T2D men had higher volumes of visceral (VAT) and subcutaneous (SAT) adipose tissue than NGT men ($p<0.001$). NGT men were also characterized by significantly higher VAT attenuation than IGT and T2D men ($p<0.001$). However, T2D men presented a significantly lower SAT attenuation that NGT and IGT men ($p<0.001$). Composition of mid-thigh muscle, reflected by the low-attenuation or normal-attenuation muscle areas, which represented muscle infiltrated with lipids or muscle with a low lipid content repectively, was similar in NGT, IGT and T2D men. Nevertheless, significant differences were observed between groups in mid-thigh deep adipose tissue attenuation, with NGT men presenting a higher deep adipose tissue attenuation than IGT and T2D men ($p<0.001$). Finally, the HOMA-IR index was only associated with VAT volume ($r=0.24$, $p=0.001$) and with VAT attenuation ($r=-0.18$, $p=0.02$) whereas subcutaneous adiposity and mid-thigh compartments showed no relationship with this marker of insulin resistance.

Conclusion These results indicate that NGT, IGT and T2D men differ in abdominal fat distribution and mid-thigh composition. Moreover, insulin resistance estimated by the HOMA-IR index seems to be more closely related to visceral adiposity than to subcutaneous adiposity or to ectopic fat deposition in the skeletal muscle. These results reinforce the relevance of measuring/estimating visceral adiposity for the identification of the subgroup of insulin resistant overweight/obese individuals.

ICAO2013-171

TOTAL BODY FAT MEASURED BY BIOIMPEDANCE AS INDICATIVE OF METABOLIC SYNDROME IN ADULTS OF A COLOMBIAN CARIBBEAN LOCATION

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Objective Browse the percentage of total body fat, determined by bioimpedance, as indicative of metabolic syndrome in adults from a village in the Colombian Caribbean.: Browse the percentage of total body fat, determined by bioimpedance, as indicative of metabolic syndrome in adults from a village in the Colombian Caribbean.

Methods Cross-sectional study. City of Soledad, Atlántico Department. n: 99 adults (pregnant women and subjects with psychomotor disease were excluded). Blood was taken in total cholesterol, HDL, triglycerides and glucose. It was measured waist circumference, height and weight (body mass index) and body fat by bioimpedance. There was metabolic syndrome criteria of the American Heart Association, ATP III, and IDF. Results were compared with and without metabolic syndrome according to the averages of total body fat obtained.
Results The average body fat percentage using were higher (p <0.05) in men and women with metabolic syndrome, using the three criteria, than in those without metabolic syndrome, other (p> 0.05) of the classification according ATP III in women, where the average fat percentage was 39.31% in those with metabolic syndrome and 37.7% in those without this condition

Conclusion Subjects with metabolic syndrome have higher mean total body fat, significantly, compared to those who do not, so you could consider the total body fat values obtained by bioimpedance as future indicators of metabolic syndrome, both by way of screening, as control.

Table 1. Average age and prevalence of metabolic syndrome in the study population, in general and by gender, in subjects participating in the municipality of Soledad

		Men (n=43)	Women (n=56)	Total (n=99)
Average age		43,9 (DE+/-:10,6)	39,5 (DE+/-:11,6)	41,38 (DE+/-:11,3)
Prevalence of metabolic syndrome	AHA	34,9%	46,4%	41,4%
	IDF	44,2%	53,6%	49,5%
	ATP III	18,6%	21,4%	20,2%
Average of total body fat	Bioimpendace	22,5 (DE+/-:6,6)	38,4 (DE+/-:7,9)	30,8 (DE+/-: 10,8)
	Siri	25,9 (DE+/-:6,5)	37,4 (DE+/-:4,05)	31,9 (DE+/-:7,9)
	Deurenberg	25,3 (DE+/-:6,5)	36,2 (DE+/-:5,2)	30,9 (DE+/-: 8,01)

Table 2. Average body fat percentages by Deurenberg equation and Siri in men and women with and without metabolic syndrome, according to three different criteria in subjects participating in the municipality of Soledad

			Men				Women				Total			
			Prom	De	t	p	Prom	De	t	p	Prom	De	t	p
Deurenberg	IDF	Yes	28,94	4,90	2,48	0,0171	38,48	5,13	2,35	0,0219	34,61	7,01	3,22	0,0017
		No	23,56	7,45			34,70	6,82			29,35	9,02		
	AHA	Yes	29,77	4,52	3,106	0,0034	39,06	5,14	2,76	0,0078	35,66	6,64	3,91	0,0002
		No	23,58	6,95			34,71	6,44			29,33	8,69		
	ATP III	Yes	30,36	5,50	2,210	0,0327	38,89	4,81	1,36	0,176	35,48	6,55	2,11	0,0367
		No	24,68	6,74			36,14	6,47			31,06	8,70		
			Men				Women				Total			
			Prom	De	t	p	Prom	De	t	p	Prom	De	t	p
Siri	IDF	Yes	29,43	5,21	2,96	0,005	39,33	3,86	2,55	0,0135	35,49	6,55	3,298	0,0014
		No	23,84	6,77			36,56	4,25			30,46	8,48		
	AHA	Yes	30,91	4,56	3,79	0,0005	39,34	3,75	2,19	0,032	36,26	5,74	3,69	0,0004
		No	23,85	6,37			36,92	4,38			30,61	8,51		
	ATP III	Yes	32,45	3,65	3,173	0,0029	39,31	2,93	1,16	0,249	36,56	4,67	2,32	0,024
		No	24,91	6,44			37,70	4,50			32,03	8,37		

Acute Coronary Syndromes

ICAO2013-101

EFFECT OF LOW W-6/W-3 FATTY ACID RATIO PALEOLITHIC STYLE DIET IN PATIENTS WITH ACUTE CORONARY SYNDROMES

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Objective Epidemiological studies indicate that high w-6 and low w-3 fatty acids in the diet may have adverse effects on cardiovascular diseases (CVDs). However, a low w-6/w-3 ratio diet by increasing w-3 and by decreasing w-6 fatty acid in the Paleolithic style diet are important.

Methods A randomized, single blind, controlled trial was carried out on 406 patients with acute coronary syndromes (ACS) diagnosed following WHO criteria. An experimental intervention group received Paleolithic style diet characterized by fruits, vegetables, whole grains, almonds and walnuts and the control group fat modified Step 1 (prudent) diet. Main outcome measures were compliance with experimental diets at one year and all cause mortality and its association with w-6/w-3 fatty acid ratio after a follow up of two years.

Results The experimental group received significantly greater amount of fruits, vegetables and whole grains, nuts and mustard oil and lower amount of refined bread, biscuits and sugar and butter and clarified butter compared to control diet group at one year of follow up. Total adherence score to Paleolithic style diet and prudent diet were significant in both the groups. Omega-6/Omega-3 fatty acid ratio of the diet which was much higher before entry to the study (32.5±3.3), was brought down to significantly lower content in the Paleolithic style diet group A (n = 204, compared to control group diet B (n = 202) at entry to the study (3.5± 0.76 vs. 24.0± 2.4 KJ/day, p<0.001). The fatty acid ratio remained significantly much lower in the experimental group compared to control group after one year of follow up (4.4±0.56 vs. 22.3±2.1,KJ/day, p<0.001). Total mortality was 14.7% in the Paleolithic style diet group and 25.2% in the control group, after a follow up of two years. The association w-6/w-3 ratio of fatty acids with mortality showed a gradient in both the groups independently, as well as among total number of deaths. A lower w-6/w-3 ratio of fatty acids; was associated with an increasing trend in mortality; 1.7% at ratio less than 5 and 19.9% at ratio 30.

Conclusion A Paleolithic style diet characterized with fruits, vegetables, nuts, whole grains and mustard oil with low w-6/w-3 fatty acids ratio <5, is more effective in causing significant decline in cardiovascular and all cause mortality compared to prudent diet in the secondary prevention of coronary artery disease. The association of mortality was consistent with increase in w-6/w-3 fatty acid ratio in the diets in both the groups and the trends were highly significant.

ICAO2013-126
EMERGENT PERCUTANEOUS REVASCULARIZATION FOR NON ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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Objective The optimal timing of invasive strategy for non-ST segment elevation myocardial infarction (NSTEMI) remains unsettled. Treatment include early vs. delayed invasive strategies. Almost 50% of patients with NSTEMI have 100% occlusion of the infarct related artery. Since there is always a chance that a NSTEMI will progress to STEMI, we determined the clinical outcomes of performing immediate PCI for NSTEMI.

Methods From January,2000 to February,2010, 653 consecutive patients with AMI underwent immediate PCI at our institution. Analysis was performed to determine if immediate PCI for NSTEMI affected clinical outcomes.

Results 467(72%) patients had STEMI and 186(28%) had NSTEMI. Median door-to-balloon time for STEMI and NSTEMI groups 75.50 and 111.50min respectively. 309(66%) and 90(48%) patients in the STEMI and NSTEMI groups had pre-TIMI 0(100% stenosis) respectively. 82(43%) patients in the NSTEMI group had LAD as the culprit lesion followed by the RCA (32%). GP IIb/IIIa (tirofiban) was used in only 36 and 17% ($p<0.001$) of patients. There were no major or minor bleeding complications in our patients. In-hospital (6 vs. 5% $p=0.190$), 30 days (1.5 vs. 1% $p=0.430$), and 1 year (3 vs. 2% $p=0.560$) mortality rates were also not significantly different. Nonfatal reinfarction at 30 days (1 event vs. none for NSTEMI), 6 months (5 vs. 2 events) and at 1 year (2 vs. 3 events) were also not significantly different. Overall ischemic driven target lesion revascularization (TLR) was also similar in both groups (19 vs. 23% $p=0.854$).

Conclusion Immediate PCI is safe in high risk patients with NSTEMI. About 50% of patients with NSTEMI had occlusive disease on angiography and may inadvertently progress to STEMI. Urgent PCI did no harm and yielded comparable early and late mortality rates, reinfarction and TLR compared with STEMI. There was a reduction in the use and infusion time of heparin and GP IIb/IIIa agents due to immediate mechanical revascularization, preventing bleeding complications. High risk patients should be treated as a case of STEMI by immediate mechanical revascularization in the earliest possible time, in order to shorten ischemic time and to allow for maximal myocardial salvage.

Adipokines

ICAO2013-122

IMPLICATION OF VISFATIN LEVELS IN PATIENTS WITH COLON CANCER

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Objective Adipocytokines have been reported to contribute to the pathogenesis of colon cancer, yet few studies have evaluated these markers. Visfatin, an adipocytokine, is thought to play a role in the pathogenesis of metabolic-syndrome-related cancers. The aim of this study was to assess the association of visfatin level with the progression of colon cancer through a case-control study.

Methods Blood levels of visfatin were measured in Saudi subjects (90 colon cancer patients and 98 controls) using enzyme-linked immunosorbent assay (ELISA) method. The two groups were matched on age, waist-to-hip ratio, race, and gender. Anthropometric measurements and blood pressure were taken. Fasting levels of glucose, insulin, and lipid profile were assayed.

Results Mann-Whitney test (Z-test) was used for comparing patient and control groups and showed that patients with colon cancer had significantly higher circulating visfatin level than the control group (4.92±2.1 vs. 2.08±1.2 ng/ml, $p < 0.0001$). Kruskal Wallis test (H teast) was used to compare the level of visfatin in different clinical stages of colon cancer and the result showed no significant differences in the level of visfatin between the colon cancer stages ($P=0.95$). Non-significant positive associations were observed for visfatin.

Conclusion The observed result indicates that visfatin is not involved with tumor stage progression but the higher level of visfatin in patients with colon cancer strengthen the results of previous studies and speculated that this adipocytokine may be a predictive or an important risk factor for colon cancer development.

ICAO2013-134

LEVELS OF SERUM ADIPONECTIN IN NON METABOLIC SYNDROME (NONMS) SUBJECTS

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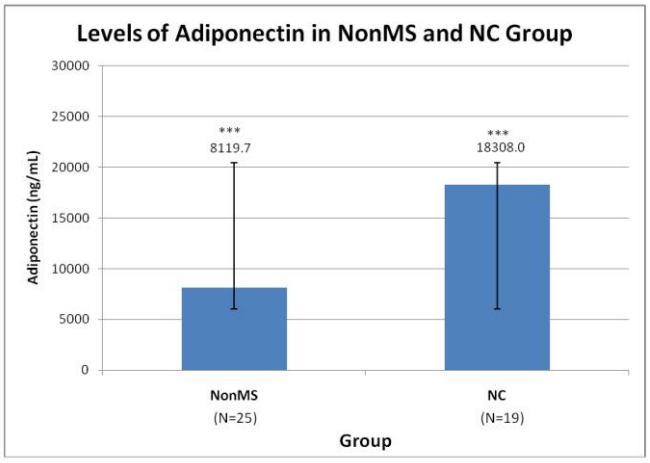
Objective Adiponectin is an anti-inflammatory protein produces exclusively by adipocytes. It has inverse correlation with obesity as define by body mass index (BMI). However, its relationship with central obesity is not much explored. This study aims to compare the levels of serum adiponectin between NonMS subjects and normal lean control subjects and to determine its association with waist.

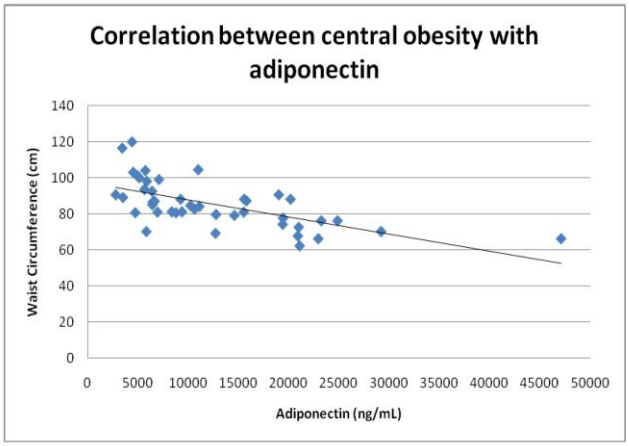
Methods A total of 44 subjects (14 males and 30 females, age (mean±SD) : 43.45±9.22) were recruited from UiTM specialist clinics and community health screenings. Anthropometric measurements and fasting blood samples were collected. Subjects were divided into NonMS and normal lean control group. NonMS diagnosis was based on the International Diabetes Federation (IDF) 2005 where subjects must be centrally obese with waist circumference ≥ 90cm or ≥ 80cm for males and females respectively with a maximum of one of other criteria; fasting plasma glucose ≥5.6mmol/L, blood pressure ≥130/85mm Hg, triglycerides level ≥1.7mmol/L and HDL-cholesterol <1.0mmol/L for males or <1.3mmol/L for females. Serum adiponectin was measured using commercially enzyme-linked immunosorbent assay (ELISA) (eBioscience, Austria).

Results A significant difference in adiponectin levels between NonMS and normal lean control group was found (mean±SD : 8119.7ng/mL ± 4522.8 vs 18308.0ng/mL ± 9718.6, p<0.0001). A negative good correlation between waist circumference and adiponectin levels was also found (p<0.001, r = -0.635).

Conclusion There is an association between central obesity and levels of adiponectin. Waist circumference is negatively correlated with levels of adiponectin in which increase waist circumference results in the decrease of serum adiponectin level.



Data are expressed as Mean ± SD, *** p<0.0001 compared to NC



There was a negative good correlation between waist circumference and adiponectin levels (p<0.001, r = -0.635).

ICAO2013-139

RESISTIN LEVELS IN CHILDREN: RELATIONSHIP WITH ANTHROPOMETRIC VARIABLES AND BODY COMPOSITION

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Objective The relationship of resistin levels with obesity remains unclear. The aim of this study was to determine resistin levels in prepubertal children and adolescents and evaluate their association with anthropometric parameters and body composition.

Methods The study population included 420 randomly selected 6- to 8-year-old children and 712 children aged 12 to 16 years. Anthropometric data were measured and body mass index (BMI) and waist-to-hip and waist-to-height ratios were calculated. Body composition was assessed using an impedance body composition analyzer. Serum resistin levels were determined using a multiplexed bead immunoassay.

Results Resistin levels were not significantly different between sexes. No significant differences in serum resistin concentrations were found between obese, overweight, and normal weight children at any age, and no significant correlations were observed between resistin concentrations and weight or BMI. However, resistin levels showed a significant positive correlation with fat mass in 12- to 16-year-old children, particularly in girls.

Conclusion In addition to describing serum resistin levels in prepubertal children and adolescents, our study suggests that resistin is related to body fat rather than to BMI in adolescents.
This work was supported by a grant from the *Fondo de Investigación Sanitaria* (FIS 11/00344).

Adipose Tissue

ICAO2013-057

LIPID METABOLISM ON IRRADIATED MOUSE MODEL

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Objective To investigate the changes of white adipose tissue and lipogenesis-related genes expression induced by radiation exposure.

Methods C57BL/6 mice were exposed to ^{137}Cs γ-rays at a single dose (5Gy) or fractionated doses (1Gy×5 times, 0.5Gy×10 times, or 0.2Gy×25 times) at the age of 2 months. After 6 months later, white adipose tissue was isolated from mouse. 2 and 25-month-old mice were studied as the young and old references. The real-time RT PCR was performed to examine the mRNA expressions of genes related to i) primary lipid metabolism (ACL, ME1 and G6PD2), ii) glucose uptake (GLUT4), iii) fatty acid synthesis (SREBP-1c, FAS and ACC), iv) triglyceride synthesis (DGAT1 and DGAT2), and v) adipose-derived hormones (LEP).

Results The weight of white adipose tissue in the irradiated group presented had tendencies to increase compared to non-irradiated group. The patterns of SREBP-1c, ACC, FAS, ACL, GLUT4, ME1 and G6PD2 mRNA levels were relatively lower in γ-irradiation groups than in non-irradiation group. The mRNA levels of leptin and DGAT are relatively higher than non-irradiation group. The alternations of these lipogenesis-related gene expressions by γ-irradiation showed a very similar pattern to those by the effects of ageing.

Conclusion The physical agent such as γ-ray could triggers the biological response resulting in the fat accumulation of white adipose tissue in mice.

ICAO2013-172

OPTIMAL CUTTING POINT FOR BODY FAT PERCENTAGE TO IDENTIFY CARDIOVASCULAR RISK FACTORS IN ADULTS FROM THREE HEALTH INSTITUTIONS

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Objective To describe optimal cutoffs of body fat percentage to identify cardiovascular risk factors in outpatient from three health institutions from the department of the Atlantic, during October to December 2011.

Methods Cross-sectional study. 581 subjects were studied three health institutions (outpatient) department of the Atlantic, who, through the estimation of body mass index and Deurenberg equation, we explored elements related cardiovascular risk factors.

Results The mean body fat in men was significantly lower (p <0.05) than in women: 27.01 vs. 37.38, and statistically significant differences were found between people with abdominal obesity, hypertension , diabetes mellitus and dyslipidemia (p <0.05).

Conclusion The average percentage of total body fat were significantly higher in subjects with cardiovascular risk factors, but further study is required to define optimal cutoffs by ROC curve analysis.

Table 1. Average body fat percentages in the study population, according to the presence of cardiovascular disease

		Prom	DE	T	P
BMI	>24,9 Kg/m2	39,77	9,97	15,49	0,000
	<25Kg/m2	25,81	8,54		
Obesity abdominal	Yes	40,05	10,08	12,69	0,000
	No	28,56	10,08		
Hypertension	Yes	36,62	10,66	3,12	0,0019
	No	33,42	12,41		
Diabetes Mellitus	Yes	39,07	9,44	2,96	0,003
	No	34,64	11,74		
Dislipidemy	Yes	36,82	10,98	3,59	0,0004
	No	33,16	11,97		

Fuente: Datos tomados por el grupo investigador. Hospital Local de Malambo, Hospital de Soledad y Clínica General del Norte

Age

ICAO2013-041

MODIFICATION OF HIGH-DENSITY LIPOPROTEINS AND INDUCTION OF DERMAL SENESCENCE USING EDIBLE AND CULINARY PENTOSE AND HEXOSE AS A SWEETENER

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Objective There has no sufficient information was reported about physiological effect of culinary pentose and hexose. This study was designed to compare induction effect of dermal senescence by pentose (ribose, xylose) and hexose (glucose, fructose) via modification of lipoproteins.

Methods Pentose and hexose (final 100 mM) were treated high-density lipoprotein and human dermal fibroblast.

Results Treatment of ribose into HDL_3 resulted disappearance of apoA-I band, suggesting a putative proteolytic degradation. However, treatment of fructose and xylose resulted to produce multimerized band, indicating that somewhat different modification mechanism between ribose and xylose. Treatment of the pentose caused the highest production of advanced glycated end products around 5- fold increased by ribose treatment. The ribose treated HDL_3 lost antioxidant ability against LDL oxidation. The ribose exhibited severe induction of dermal senescence in human dermal fibroblast cell.

Conclusion In conclusion, among the hexose and pentose, ribose showed the most severe glycation effect and induction of dermal senescence. (Park JS and Kim SM are co-first authors.)

Cardiometabolic Risk

ICAO2013-033
ASSOCIATION OF SERUM PHOSPHOLIPID PUFAS WITH CARDIOMETABOLIC RISK: BENEFICIAL EFFECT OF DOCOSAHEXAENOIC ACID ON REDUCED VASCULAR PROLIFERATION AND CELLULAR INFLAMMATION

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Objective Cardiovascular disease was reported to be associated with blood or dietary polyunsaturated fatty acids (PUFAs). Particularly, w3-PUFAs were known for cardioprotective effect. However, the results are still controversial. We aimed to clarify the association of serum phospholipid PUFAs with cardiometabolic risk through case-control and experimental studies.

Methods Serum phospholipid FA compositions and cardiometabolic risk parameters were measured in controls [healthy: n=987, metabolic syndrome (MetS): n=214] and CAD patients (CAD only: n=152, CAD with MetS: n=56). Experimental assays were additionally performed in vascular smooth muscle cells (VSMCs).

Results Major cardiometabolic risk related markers, i.e, insulin resistance (IR), high sensitive C-reactive proteins (hs-CRP) were higher, and plasma adiponectin and LDL particle size were lower in CAD patients, particularly in those carrying MetS than healthy controls. Serum linoleic acid (LA, C18:2w-6) was lowest and dihomo-g-linolenic acids (DGLAs, C20:3w-6) was highest in CAD patients with MetS among the 4 groups. Docosahexaenoic acid (DHA, C22:6w-3) was lower and arachidonic acid (AA, C20:4w-6) and w6/w3-PUFAs were higher in CAD patients than controls. w3-PUFAs were significantly lower in CAD patients, particularly in those with MetS than healthy controls. Multiple regression analysis revealed that AA and DHA mainly contributed to the increased or decreased cardiometabolic risk (adjusted b-coefficients for AA: 0.336; for DHA: -0.296) together with age, MetS factors, LA, DGLA and gender ($r=0.529$, $p<0.001$). Additionally, LA and DHA significantly suppressed VSMC proliferation, and DHA dramatically inhibited NF-κB p65 nuclear translocation, which is associated with inflammatory response.

Conclusion Among serum phospholipid PUFAs, AA and DHA were mainly associated with cardiometabolic risk. Particularly, DHA showed a beneficial effect on reduced vascular proliferation and inflammation.

ICAO2013-071

THE RELATIONSHIP BETWEEN CONSUMING DIFFERENT TYPES OF OILS AND APO A AND APO B LEVELS

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Objective Using different oils in cooking leads to different oxidative effects in their products especially under cooking conditions at home. Diet is considered as an important predictor of dyslipidemia. Epidemiologic studies have indicated that receiving partial-hydrogenated oils is associated with coronary heart disease (CHD).Apolipoprotein B (Apo B) lipoprotein a [LP(a)] is the main protein component of LDL-c and is a better index for diagnosis of patients at the risk of cardiovascular diseases (CVD) than triglyceride and cholesterol.

Methods Isfahan Healthy Heart Program was a community-based intervention to modify CVD risk factors and promote lifestyle. It was implemented during 2001-07. The present study was conducted on 171 and 117 taxi drivers who have been randomly selected in 2001 and 2007, respectively. The subjects were selected from 6175 and 4719 participants of the first and third phases of Healthy Heart Program, respectively. Subjects underwent several interventions to prevent CVD risk factors and modify their lifestyle during six years. All the studied subjects were evaluated at the first and third phases of Isfahan Healthy Heart Program in terms of demographic factors and physical factors including blood pressure and biochemical examinations. In addition, blood samples were tested for biochemical factors.

Results In our male participants, there were positive correlations between Apo B levels and consumption of olive oil, butter, and cream. Significant inverse correlations were observed between Apo B/A ratio and consumption of olive oil, butter, and cream. Among women, Apo A was positively correlated with consumption of hydrogenated oils and butter and negatively correlated with consumption of liquid oil. The mentioned relationships were all statistically significant. There was a significant inverse correlation between Apo B and consumption of liquid oil. Moreover, Apo B/A ratio and consumption of butter and cream had significant inverse correlations.The Apo B/A ratio was significantly related with consumption of butter and cream.

Conclusion It was seen that consumption of butter and cream caused no problems in men, women, and the whole community. Consumption of olive oil was useful only among men. However, its positive effects in women and the whole community were not significant.

ICAO2013-089

ASSOCIATION OF FATTY LIVER INDEX AS AN INDICATOR FOR HEPATIC STEATOSIS AND SUBCLINICAL CORONARY ARTERY ATHEROSCLEROSIS

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Objective Fatty liver disease (FLD), especially nonalcoholic fatty liver disease, are frequently associated with risk factors for atherosclerosis such as hypertension, obesity, diabetes, dyslipidemia, and insulin resistance. Recently, a simple scoring system called fatty liver index (FLI) was developed as a predictive indicator of FLD. FLI was calculated using an equation that considers serum triglyceride levels, gamma-glutamyltransferase, waist circumference, and body mass index. In this study, we aimed to evaluate whether FLI can be useful tool for the detection of subclinical coronary atherosclerosis detected by coronary multidetector computed tomography (MDCT) in an asymptomatic population.

Methods We collected the data of asymptomatic 1,272 subjects (759 men and 513 women ≥20 yr of age; mean age 52.8 yr) who participated in a routine health screening examination of Asan Medical Center (Seoul, Republic of Korea). Significant coronary artery stenosis defined as >50% stenosis. The Agatston score was used as the coronary artery calcium score (CACS) and was calculated and categorized as followings: CACS ≤100 (none to mild) and CACS >100 (moderate to severe).

Results We could observe that more subjects with significant coronary stenosis and moderate to severe CACS were included in the group with FLI≥60 (FLI +) than in the group with FLI <20 (FLI -). The odds ratios (ORs) for the presence of significant coronary stenosis and moderate to severe CACS were significantly higher in the group with FLI≥60 (FLI +) than in the group with FLI <20 (FLI -) even after adjustment for various confounding variable including surrogate measure of insulin resistance.

Conclusion Our results suggest that FLI as a simple surrogate indicator of hepatic steatosis can be useful in identifying subjects with significant subclinical coronary atherosclerosis.

ICAO2013-128

CHANGE IN ABSOLUTE FASTING GLUCOSE 12 MONTH AFTER PCI WITH THE DEVELOPMENT OF MACE IN DES-IMPLANTED PATIENTS ON STATIN THERAPY

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Objective Statin therapy for the prevention of CVD is known to be as diabetogenic. But most clinical trials suggested that current statin therapy in patients with moderate to high cardiovascular risk should not be changed, due to the outwheighing benefits of statin on CVD prevention. We investigated which clinical variable on treatment, including glycemic parameters, is most closely associated with the development of 24 month MACE(all death, any myocardial infarction and target vessel revascularization) in DES implanted patients on statin therapy.

Methods Total 299 patients undergone DES implantation on coronary heart disease with taking statins for secondary prevention were involved. Tracking the development of MACE within 24 month post-PCI, 12 month follow up clinical variables showing close correlation to the event development were evaluated. To discover whether the degree of time dependent changes of clinical parameters are associated with the event development, subtractions from baseline to follow up lab results are obtained, and also analyzed after absolute value conversion. Variables showing significant difference between the groups were put into the multivariate analysis, to figure out further clinical relevance.

Results During the follow up, 46 (15.3%) MACE cases were developed. Fasting glucose and HbA1c at 12 month follow up were significantly higher in the event group. Subtraction variables representing change from baseline to follow up lab showed no significant differences, however, when absolute values of subtraction variables are analyzed, fasting glucose variance during 12 month post-PCI showed significant correlation to the event development. In multivariate analysis, patients showing higher absolute change of fasting glucose greater than 17mg/dL/year were significantly associated with the increased risk of MACE development. Survivals curve analysis also figured out higher MACE development in such patients showing greater 12 month fasting glucose variance.

Conclusion The findings suggest that higher absolute change of fasting glucose during 12 month post-PCI is independently associated with increased risk of 24 month MACE in DES implanted patients on statin therapy. Statin-related relative glucose control impairment described as absolute fasting glucose change in the current study might be responsible for the development of 24 month MACE.

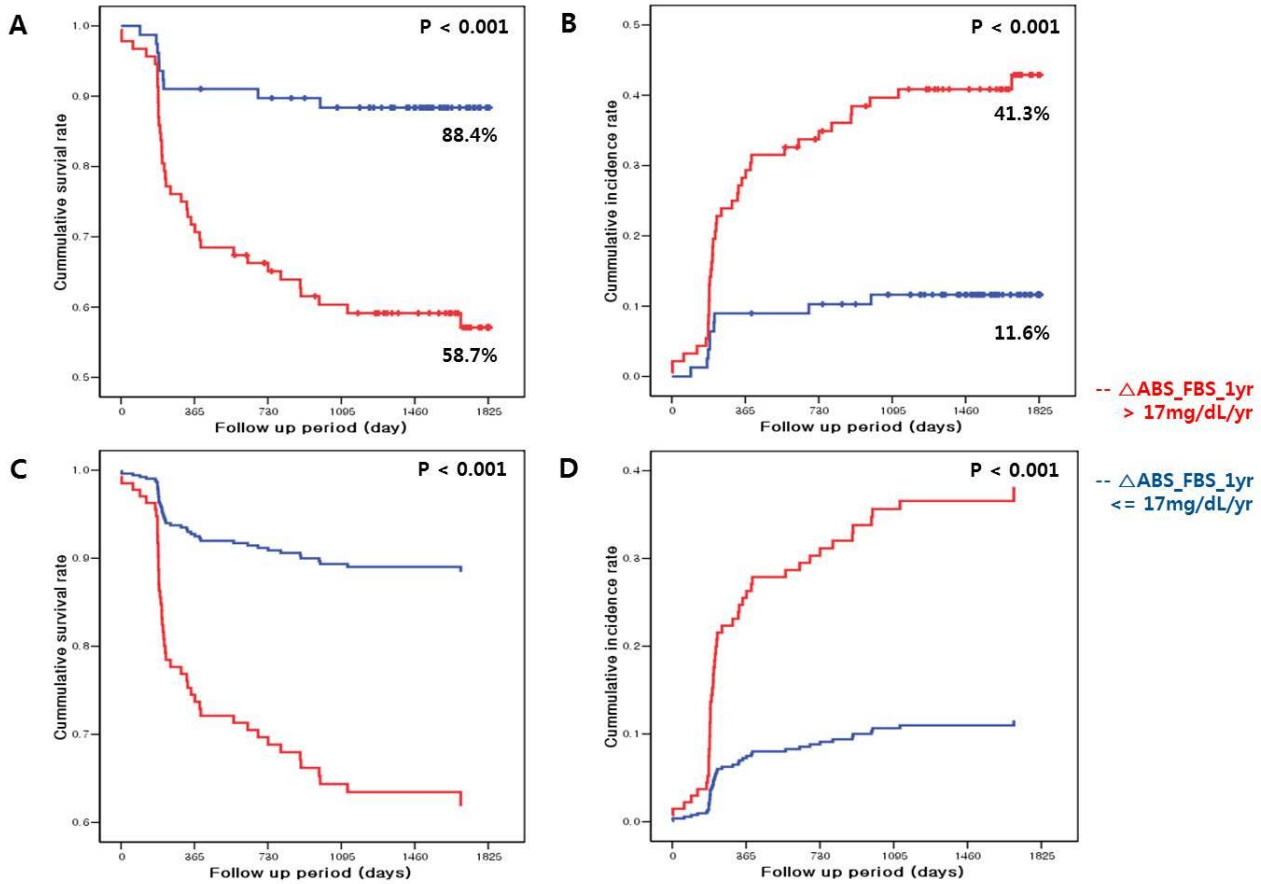

Figure 1. A,B: Five-year Kaplan-meier survival curve for MACE development. C,D: Five-year cox-proportional hazard model for MACE devlopment.
* Included variables: Age, gender, underlying Hypertension, Non-ST elevation myocardial infarction at admission, Low density lipoprotein cholesterol at 1year follow up, Absolute fasting glucose change in 1 year follow up);
**△ABS_FBS_1yr: Absolute fasting glucose change in 1 year follow up; MACE: Major adverse cardiovascular events.

	Model 1		Model 2	
Variables	Adjusted OR (95% C.I)	P-value	Adjusted OR (95% C.I)	P-value
Gender (male)	1.05 (0.49 - 2.266)	0.892	1.06 (0.49 - 2.316)	0.875
Age	0.99 (0.96 - 1.028)	0.726	0.99 (0.96 - 1.028)	0.633
Hypertension	2.07 (0.94 - 4.538)	0.069	1.95 (0.98 - 4.704)	0.097
Non-STEMI at admission	2.58 (1.21 - 5.480)	0.013	2.44 (1.30 - 6.021)	0.021
LDLc at 1 year follow up	0.98 (0.97 - 1.001)	0.094	0.98 (0.97 - 1.000)	0.113
ΔABS_FBS_1yr (+ 10mg/dL/yr)	1.05 (1.00 - 1.116)	0.036		
ΔABS_FBS_1yr (> 17mg/dL/yr)			2.83 (0.84 - 8.030)	0.008

Table 1. Multivariate analysis for 24 month MACE development.
* STEMI: ST elevation myocardial infarction; LDLc: Low density lipoprotein cholesterol, △ABS_FBS_1yr: Absolute fasting glucose change in 1 year follow up; MACE: Major adverse cardiovascular events.
** 24 month MACE: all death, any myocardial infarction, target vessel revascularization within 24 month.

ICAO2013-164

INCREASED PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN SUBJECTS WITH INTRACRANIAL ATHEROSCLEROSIS DETECTED IN TRANSCRANIAL DOPPLER SONOGRAM

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Objective Non-alcoholic fatty live disease (NAFLD) is considered as the risk for cardiovascular disease. Intracranial atherosclerosis (ICA) is the cause for ischemic stroke and other cerebrovascular diseases. Transcranial Doppler ultrasonogram (TCD) is a diagnostic modality that could be noninvasively used for the diagnosis of ischemic cerebral arteries. In this study, we analyzed the relationship between NAFLD and ICA assessed by TCD in apparently healthy Korean adults.

Methods TCD was performed to assess the status of cerebral arteries as a part of a health screening program. Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial methods was used to diagnose ICA with TCD. The presence of NAFLD was assessed by abdominal ultrasonogram. Analyses were performed in 74 subjects with abnormal TCD finding and 147 age- and body mass index (BMI)-matched control subjects.

Results In total of 221 participants, 107 subjects (48.4%) were men and mean age was 49 years. Among the subjects, 51 subjects (23.1%) showed NAFLD detected by abdominal ultrasonogram. Subjects with NAFLD were metabolically worse compared with subjects with normal liver. When the subjects with NAFLD were compared between the groups, the proportion of NAFLD subjects was higher in group with ICA compared with subjects without ICA (31.1 vs 19.0%, p=0.032). In reverse, proportion of subjects with ICA was higher in group with NAFLD compared with subjects without NAFLD (45.1 vs. 30.0%).

Conclusion Subjects with NAFLD showed significantly higher trend for ICA detected by TCD in this apparently healthy subjects, suggesting the association of ICA and NAFLD.

ICAO2013-168

CENTRAL OBESITY IN PATIENTS WITH METABOLIC SYNDROME IS RELATED TO EARLY VASCULAR AGING: DATA FROM A CROSS-SECTIONAL LITHIR STUDY

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Objective Metabolic syndrome (MetS) patients are at increased cardiovascular risk, but the exact mediation of the risk remains a matter of controversy. Obesity and various clusters of the metabolic syndrome components are considered, but large-scale studies are lacking. Therefore we aimed to investigate predictive value of obesity on the arterial markers as a surrogate endpoint of cardiovascular risk.

Methods A cross-sectional study was carried among 3620 MetS subjects (aged 54±7, 60% women) of LitHir primary prevention study. MetS was diagnosed according to the updated NCEP ATP III criteria. Markers of early vascular aging were estimated as a surrogate endpoint of cardiovascular risk. Aortic stiffness was assessed as carotid to femoral pulse wave velocity (cfPWV) and ankle-brachial stiffness index (CAVI), carotid stiffness index (CSI) and intima media thickness (IMT) were measured by echo-tracking. Endothelial function was evaluated by peripheral arterial tonometry as reactive hyperemia index (RHI). All subjects underwent oral glucose tolerance test (OGTT) with measurement of plasma fasting and 2 h glucose and insulin.

Results In our study group, MetS subjects with central obesity (89% of all pts) had higher fasting plasma glucose (6.2±1.3 vs. 5.9±0.9 mmol/l, p<0.0001), OGTT plasma glucose (6.6±2.4 vs 5.6±2.0 mmol/l, p<0.0001), fasting plasma insulin (95.5±58.8 vs. 64.3±33.0 pmol/L, p<0.0001) and OGTT insulin (383.0±334.6 vs. 216.9±195.5 pmol/L, p<0.0001). Glycated hemoglobin and mean arterial pressure were also slightly greater in subjects with central obesity (respectively, 5.9±0.6 vs. 5.7±0.5% and 107±13 vs. 103±12 mmHg, both with p<0.001). MetS subjects with central obesity as compared to those without central obesity had stiffer carotid arteries (CSI 4.21.6 vs. 3.41.3, p<0.001), stiffer aorta (cfPWV 8.8±1.6 vs. 8.2±1.8 m/s, p<0.001) and higher IMT (673±104 vs. 646±112 µm, p<0.001). Multivariate analysis revealed that measure of central obesity as continuous but not categorical variable (based on updated NCEP ATP III criteria) remained a significant predictor of early arterial aging after adjusting for other risk factors.

Conclusion Our cross-sectional study shows that central obesity is a significant determinant of the variability of arterial parameters in MetS subjects. It suggests that patients with central obesity are prone to early vascular aging, a surrogate marker of cardiovascular risk.

Cardiovascular Disease

ICAO2013-025

SCOPARONE, CHINESE HERBAL COMPOUND PREVENTS VASCULAR REMODELING VIA THE INTERFERENCE OF STAT3 ACTIVITY

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Objective The preventative for the abnormal proliferation and migration of vascular smooth muscle cells(VSMCs) is critical for the patients suffering with atherosclerosis, diabetes, hypertension, stroke and coronary artery disease. Recently, scoparone is a major constituent of Chinese herb *Artemisia Capillaries* that has been the beneficial agents as anticoagulant, hypolipidemic, vasorelaxant, anti-oxidant and anti-inflammation including the traditional treatment of neonatal jaundice in Asia. In our study, we investigate the mechanism that scoparone can suppress the vascular remodeling via the anti-proliferative pathway.

Methods The thoracic aorta of 4-week-old SD rats was used for primary culture of VSMCs. The migration and proliferation by razor-blade scrapping and 20%FBS induction were measured in the presence of scoparone. FACS analysis and western blotting were carried out for cell cycle determination. The promoter activities were assessed by luciferase reporter *in vitro*. We evaluated the phosphorylated-STAT3 induced by PDGF treatments in C2C12 cells overexpressing STAT3 or constitutive active STAT3. Immunofluorescent staining with pSTAT3 (Y705) was performed for determining the localization of STAT3 in scoparone treated VSMCs.

Results The proliferation and migration of VSMCs were significantly attenuated by scoparone in time and dose dependent manners. Scoparone reduced dramatically the serum-stimulated accumulation of cells in S phase and increased cell numbers in G0/G1 phase concomitantly, but not apoptosis in VSMCs, consistent with decreased expression of cyclin D_1 and phsphorylated Rb. MMP9 promoter activity and phosphorylated STAT3 was significantly reduced by scoparone. Interestingly, scoparone attenuated the enhanced cyclin D promoter activity by both WT and active form of STAT3. Similarly, cell proliferation markers by PDGF was decreased by scoparone, while, scoparone had no effect on PDGF-induced phosphorylation of JAK2 and Src. Based on immunofluorescent staining, phosphorylated STAT3 proteins by PDGF were predominantly localized in the nucleus, which markedly reduced in scoparone-treated cells.

Conclusion Scoparone suppresses VSMC proliferation through G1 phase arrest by inhibiting Rb phosphorylation and it blocks the accumulation of STAT3 from the cytosol to nucleus, independent of the STAT3 form and upstream like Jak and Src which leads to vascular remodeling by growth factor induction. We provide the evidence that scoparone may be new preventive agent for treating the increasing cardiovascular patients.

ICAO2013-061

SERUM ALKALINE PHOSPHATASE IS A PREDICTOR OF MORTALITY, MYOCARDIAL INFARCTION, OR STENT THROMBOSIS AFTER IMPLANTATION OF CORONARY DRUG-ELUTING STENT

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Objective The association between ALP and mortality was reported in several subgroups of patients. But, the role of ALP in overall CAD patients after PCI remains unknown. The aim of this study was to examine the prognostic value of alkaline phosphatase (ALP) level in patients with coronary artery disease (CAD) who underwent percutaneous coronary intervention (PCI) with drug-eluting stent (DES).

Methods We prospectively included CAD patients who underwent PCI with DES. After exclusion of patients with liver disease and cancer, 1,636 patients were selected for the analysis of clinical outcomes (median duration of follow-up; 762 days, interquartile range; 494-1068 days), and were classified into tertiles by baseline measurements of ALP (<63, 63-78, and >78 IU/L).

Results After adjustment of potential confounders including angiographic data, the independent and dose-dependent association was observed between tertile of ALP and the adjusted hazard ratio (HR) of all-cause mortality (*p* for trend<0.0001). Specifically, compared to the lowest ALP tertile, the adjusted HR of all-cause mortality in the highest tertile was 4.21 (95% confidence interval 2.03-8.71). When restricted cubic spline regression was used to explore the adjusted association between ALP and all-cause mortality, we observed an approximately linear increase in hazard of mortality as ALP levels get higher [Figure 1]. In subgroup of patients with stable or unstable angina, a similar association was noted (*p* for trend<0.0001). In terms of cardiovascular mortality, myocardial infarction, and stent thrombosis, the adjusted HRs in the highest ALP tertile were 3.92 (1.37-11.20), 1.98 (0.91-4.29), and 2.73 (1.33-5.61), respectively, compared with the lowest tertile. Furthermore, evaluation of both ALP and C-reactive protein provided better predictive value than either alone. Interesting result suggesting the mechanism was that ALP was significantly associated with the presence of angiographic coronary calcification (*p* for trend=0.046) [Figure 2].

Conclusion Our study demonstrated that the higher serum ALP level is an independent predictor of mortality, myocardial infarction, and stent thrombosis in CAD patients after PCI with DES.

Figure 1.

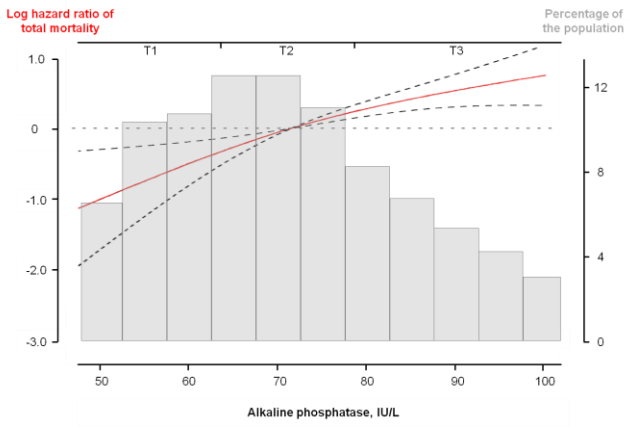
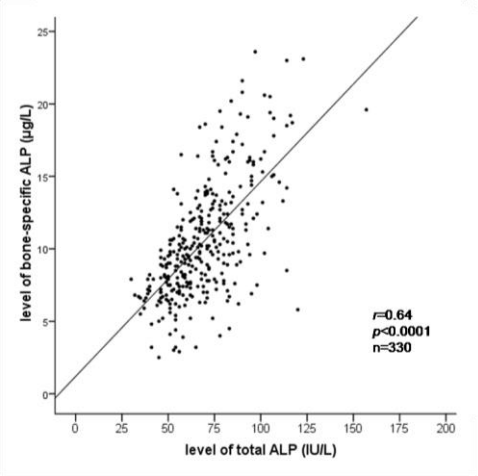


Figure 2.



ICAO2013-090

THE PREVENTIVE EFFECT OF UNCARBOXYLATED OSTEOCALCIN AGAINST FREE FATTY ACID-INDUCED ENDOTHELIAL APOPTOSIS THROUGH THE ACTIVATION OF PI3-KINASE/AKT SIGNALING PATHWAY

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Objective Increasing evidence suggests that osteocalcin (OC), one of the osteoblast-specific proteins, has been associated with atherosclerosis, but conflicting results. The aim of this study was to elucidate the independent effect of uncarboxylated osteocalcin (ucOC), an active form of osteocalcin which has been suggested to have an insulin sensitizing effect, on vascular endothelial cells.

Methods We used human aortic endothelial cells and treated them with ucOC. Linoleic acid (LA) was used as a representative free fatty acid. Apoptosis was evaluated using various methods including a terminal deoxyribonucleotide transferase-mediated deoxyuridine triphosphate nick-end labeling analysis kit and Western blotting for cleaved caspase 3, cleaved poly (ADP-ribose) polymerase and Bcl-xL. The phosphorylations of Akt and endothelial nitric oxide synthase (eNOS) as well as the level of NO were measured to confirm the effect of ucOC on insulin signaling pathway.

Results Pretreatment of ucOC (30 ng/ml) prevented LA-induced apoptosis in insulin-stimulated endothelial cells, which effects were abolished by pretreatment with the phosphatidylinositol 3-kinase (PI3-kinase) inhibitor, wortmannin. Treatment of ucOC (ranged from 0.3 to 30 ng/ml) significantly increased the phosphorylation of Akt and eNOS and nitric oxide secretion from endothelial cells in a PI3-kinase dependent manner.

Conclusion Our study is the first to demonstrate the independent effect of ucOC on vascular endothelial cells. Our results further suggest that ucOC could have beneficial effects on the atherosclerosis.

ICAO2013-095

TETRAHYDROBIOPTERIN ENHANCED CARDIAC CONTRACTILITY IN TYPE 2 DIABETIC RAT VIA MITOCHONDRIAL MODULATION

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Objective Tetrahydrobiopterin (BH_4) is a multifunctional co-factor having potential to regulation mitochondria function including biogenesis and oxidative phosphorylation. Diabetic cardiomyopathy is the major cause of mortality and morbidity in diabetes mellitus patients. Mitochondrial dysfunction has a significant role in the development and complications of diabetic cardiomyopathy.

The objectives of this study is to test the mitochondria mediated therapeutic potential of BH_4 in the treatment of diabetic cardiomyopathy

Methods Fifty weeks aged LETO and OLETF rats were used as control and type 2 diabetes animal models respectively. Onset of diabetes was confirmed by intravenous glucose tolerance test (IGTT). Randomly selected OLETFs were administrated BH_4 20mg/kg/day bolus i.p. during 2 weeks (OLETF/BH_4).

Results Administration of BH_4 did not altered IGTT, body weight or blood component of OLETF. Echocardiography revealed dilated dysfunction in OLETF and OLETF/BH_4 model compared to LETO. BH_4 treatment significantly increased left ventricular contractility in OLETF resulting in enhanced ejection fraction and fractional shortening. Mitochondrial membrane potential, electron transport chain complex activity and ATP concentration were decreased in OLETF model and BH_4 treatment successfully restored those. Interestingly, increased oxidative stress in OLETF heart tissues were significantly attenuated by BH_4 treatment. RT-PCR and western blot analysis showed that BH_4 treatment restored several mitochondrial protein alterations in type 2 diabetic heart.

Conclusion These results suggest that BH_4 has therapeutic potential which corrected mitochondrial dysfunction resulting enhancement of LV contractility in diabetic cardiomyopathy.

ICAO2013-136

DIAGNOSIS OF FAMILAL HYPERCHOLESTEROLAEMIA BY DUTCH LIPID CLINIC AND US MEDPED CRITERIA AMONG SIMON BROOME POSITIVE FH CASES

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Introduction Early and accurate diagnosis of FH is important as it carries a high risk of developing premature coronary artery disease (CAD).

Objective To investigate the identification of FH by the Dutch Lipid Clinic Criteria (DLCC) and US MedPed criteria among FH subjects who fulfilled the Simon Broome's criteria (SB).

Methods: Subjects were recruited from the Specialist Lipid and Family Medicine Clinics and health screening programmes. Fasting serum and plasma samples were collected for the measurement of lipid profile, renal profile, liver function test, thyroid function test and glucose done on automated analyzers (Roche 400, Cobas Integra, USA and Centaur XP, Siemens, USA). Diagnosis of FH was made if secondary causes of hypercholesterolaemia was excluded, had a total cholesterol (TC) level ≥ 7.5mmol/L and/or low lipoprotein cholesterol (LDL-c) level of ≥ 4.9mmol/L and fulfilled the other criteria set by SB. Diagnosed FH by SB were then compared with the diagnostic criteria of DLCC and US MedPed.

Results 202 FH subjects diagnosed by the SB criteria were recruited. Among the definite FH by SB (149/202); 103(51.0%), 22 (10.9%), 19 (9.4%) and 5(2.4%) were definite, probable, possible and not FH respectively according to the DLCC. Among the possible FH by SB (42/202), 2 (1.0%), 4 (2.0%) and 36 (17.8%) were definite, probable and possible FH respectively according to the DLCC. There are 11(5.5%) of possible DLCC not categorized in any SB criteria. Among the definite FH by SB (149/202), 46 (22.7%) and 103 (51.0%) were FH and non-FH respectively according to the US MedPed criteria. Among the possible FH by SB (42/202), 3 (1.6%) and 39(19.3%) were FH and non-FH respectively according to the US MedPed criteria. Among the entire 202 FH subjects by SB, 186 (92.1%) were FH by DLCC but only 49 (24.3%) were FH by US MedPed.

Conclusion The SB and DLCC are in agreement in the identification of FH but the US MedPed criteria underdiagnosed FH among SB positive FH cases.

1) SB compared to DLCC

SB / DLCC	Definite (Percentage)	Possible (Percentage)	No FH (Percentage)	Total (Percentage)
Definite	103 (51.0)	2 (1.0)	0 (0.0)	105 (52.0)
Probable	22 (10.9)	4 (2.0)	0 (0.0)	26 (12.9)
Possible	19 (9.4)	36 (17.8)	11 (5.5)	66 (32.6)
No FH	5 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Total	149 (74)	42 (21)	11 (5)	202 (100.0)

2) SB compared to USMedped

SB / USMedped	Definite (Percentage)	Possible (Percentage)	No FH (Percentage)	Total (Percentage)
FH	46 (22.7)	3 (1.6)	0 (0.0)	49 (24.3)
Not FH	103 (51.0)	39 (19.3)	11 (5.4)	153 (75.7)
Total	149 (74)	42 (21)	11 (5)	202 (100.0)

ICAO2013-138

THERAPEUTIC EFFECT OF SHOCKWAVE IN ATHEROSCLEROSIS

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Objective Excessive lipid accumulation by macrophages plays a crucial role in atherosclerosis. Foam cells are generated by uncontrolled uptake of modified LDL, especially oxidized LDL (oxLDL), and/or impaired cholesterol efflux mediated by ATP-binding cassette (ABC) family transporters, ABCA-1 and ABCG-1. Shockwave, elicited by transient pressure disturbance, have been used for extracorporeal lithotripsy or for treating musculoskeletal disorders. Our goal is to investigate of therapeutic effect of shockwave in atherogenic process.

Methods Murine peritoneal macrophages were exposed to shockwaves at 0.04 mJ/mm^2 with 1000 impulses, lysed after 6, 18 and 24 hours, and tested for expression of ABCA-1. Also, mRNA level of ABCA-1 was tested by semi-quantitative RT-PCR. Measurement of intracellular cholesterol, Oil-red O staining, migration assay were performed.

Results The western blot showed that shockwave induced 2.0-2.8 fold increase of ABCA-1 within 18-24 hours. mRNA levels of ABCA-1 was also increased by shockwave with 2.0 fold of peak increase in 18 hours. The increased expression of ABCA-1 was mediated by phosphorylation of ERK 1/2 (Tyr204). Western blot analysis revealed that shockwave induced phosphorylation of ERK 1/2 (Tyr204) in murine macrophages. Shockwave-induced increase of ABCA-1 was blocked by U0126 (40μM), a specific inhibitor for ERK. Oil-red O staining showed that macrophages exposed to shockwave had 25% less intracellular lipid droplets. Intracellular cholesterol measured by cholesterol oxidase and esterase revealed that macrophages exposed to shockwave had 23% less intracellular cholesterol when incubated with oxLDL (50μg/ml) for 16 hours. In vitro migration assays including modified Boyden chamber migration assay and scratch wound healing migration assay showed that macrophages exposed to shockwave had 1.2 fold more migration and had diminished migration-inhibitory effect of oxLDL.

Conclusion Shockwave reduces macrophage foam cell formation via ERK-mediated increase of ABCA-1 mediating lipid efflux and promotes macrophage migration which may induce macrophage egress from atherosclerotic lesion. Our study suggests anti-atherogenic effects of shockwave as a potential treatment modality for atherosclerosis.

ICAO2013-144

MODIFICATION OF LIPOPROTEINS BY BLOOD LEAD (PB) TO RESULT SKIN TOXICITY AND PRO-ATHEROGENIC EFFECT IN HUMAN CELLS AND ZEBRAFISH MODEL

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Objective Lead (Pb) is one of heavy metals that can be easily contaminated through such as food and cosmetics. Although a lot of research about the Pb toxicity has been known, however its effect of skin toxicity and cardiovascular disease is still not unknown. In this study, physiological toxicity of the Pb was studied on human cells (macrophage, dermal fibroblast) and zebrafish.

Methods The Pb was treated to human high-density lipoprotein (HDL) and low-density lipoprotein (LDL) either normal blood concentration (85 nM) or high concentration as disease state (2 μM). Zebrafish adults and embryo were exposed to Pb (final 0.03 and 0.66 ppm) under consuming normal diet (ND) or high cholesterol diet (HCD).

Results Treatment of Pb (final 2 μM) induced oxidation and modification on HDL and LDL. Cellular uptake of acetylated LDL into macrophages and severe senescence in human dermal fibroblast (HDF) cell was accelerated by the Pb treatment. After 4 weeks soaking in water containing Pb, ND groups showed that elevated 16% and 33% of serum total cholesterol (TC) and triglyceride (TG), respectively. Serum glucose was elevated with hepatic inflammation by the higher Pb exposure in water; 36% and 174% of increase in glutamic oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT). Zebrafish embryos, which were exposed to the Pb 16.5 ppm, showed abnormal development.

Conclusion Treatment of Pb induces modification of lipoproteins, senescence and toxicity on HDF cell. In zebrafish adult, Pb can cause hyperlipidemia and hepatic toxicity. Exposure of Pb causes embryo toxicity with attenuation of developmental speed.

ICAO2013-147

EXPOSURE OF MERCURY CAUSE ATHEROSCLEROTIC PROCESS AND SKIN AGING IN HUMAN CELLS AND ZEBRAFISH

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Objective Higher concentration of mercury (Hg) in blood are well known with incidence of many neurodegenerative disease. The toxicity of Hg in atherosclerosis and skin aging has not been clearly known. In this study, we investigated the cardiovascular and dermal risk of Hg exposure in human lipoprotein.

Methods The Hg was treated to human plasma apolipoprotein (apoA-I) and high density lipoprotein (HDL). Treatment of mercury into human macrophage and dermal fibroblast cell either normal (final 74 nM) or high (final 1.4 μM) blood concentration as disease state. Zebrafish adults were exposed to Hg (final 0.02 and 0.4 ppm) for 3 weeks under consuming normal diet (ND) or high cholesterol diet (HCD).

Results Treatment of Hg caused multimerization of plasma apoA-I and HDL and more acceleration of low-density lipoprotein (LDL) uptake into macrophage with premature dermal cell senescence. After 3 weeks exposure of zebrafish adult in water containing Hg, ND groups showed that 90% and 14% elevated serum total cholesterol (TC) and triglyceride (TG), respectively. In the same manner, HCD groups showed that 135% and 22% elevated TC and TG, respectively. By the exposure in zebrafish, increased oxidative stress with fatty liver change and skin aging in zebrafish trunke.

Conclusion Mercury (Hg) exposure caused modification of lipoprotein and acceleration of atherosclerotic process and skin aging in zebrafish.

Childhood Obesity

ICAO2013-114

PLASMA NON-ESTERIFIED FATTY ACID LEVELS IN CHILDREN AND THEIR RELATIONSHIP WITH SEX STEROIDS

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Objective Puberty is associated with decreased insulin sensitivity. Sexual hormone levels have been related with the onset of insulin resistance, but their relationship with non-esterified fatty acids (NEFA) remains unexplored. The aim of this study was to evaluate circulating NEFA levels in population-based samples of prepubertal children and adolescents and to analyze the association of NEFA with obesity, insulin resistance, and sexual hormones in adolescents.

Methods The studied population included 854 randomly selected 6- to 8- year-old children and 822 children aged 12 to 16 years. NEFA levels were determined using a commercial kit. Testosterone and estradiol levels were determined by RIA, and insulin and sex hormone binding protein by IRMA. HOMA was calculated as an indicator of insulin resistance.

Results NEFA levels were lower in adolescents than in 6- to 8-year-old children, and decreased progressively with age between 12-year-olds and 16-year-olds. No significant differences in NEFA levels were observed between obese and non-obese children. NEFA levels did not correlate with BMI in any gender. NEFA were not correlated with insulin or HOMA in girls, and appear negatively correlated with these variables in boys. Insulin and HOMA were negatively correlated with SHBG levels in both sexes adjusting by age but NEFA levels were not (table 1).

Conclusion NEFA levels decrease with age in adolescents and are not significantly increased in obese children, supporting the fact that the decreased insulin sensitivity at this age is not affecting NEFA metabolism. Although SHBG is related to insulin and HOMA independently of age in both sexes, SHBG levels are not associated with NEFA.
This work was supported by a grant from the *Fondo de Investigación Sanitaria* (FIS 11/00344).

Table 1. Spearman correlation analysis by gender

	Boys				Girls		
	NEFA	Insulin	HOMA		NEFA	Insulin	HOMA
NEFA	-	-.132**	-.120*	NEFA	-	-.045	.008
BMI	.005	.161**	.189***	BMI	.024	.208***	.225***
Testosterone	.089	.064	.056	Estradiol	.026	.036	.031
SHBG	.001	-.142**	-.144**	SHBG	-.025	-.264***	-.282***

* p<0.05, ** p<0.01, ***p<0.001

Clinical Trials

ICAO2013-146

THE EFFECTS OF LIRAGLUTIDE ON PALATABILITY AND AD LIBITUM ENERGY INTAKE IN OBESE ADULTS WITHOUT DIABETES

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Objective The effects of liraglutide on meal palatability in obese individuals are unknown.

Methods In this double-blind, incomplete 2-period crossover trial, participants (n=49, age 48.3±13.2 years, BMI 34.2±2.7 kg/m^2 [mean±SD]) were randomised to 5 weeks of treatment with once-daily s.c. liraglutide 1.8 mg, 3.0 mg, or placebo. After each 5-week period, a 5-hour meal test was performed. Appetite ratings, meal palatability (*post-hoc* analysis), nausea and well-being were assessed using visual analogue scales (0–100 mm) following an energy-fixed breakfast. Energy intake and palatability at a subsequent *ad libitum* lunch were also measured.

Results No statistically significant treatment differences in mean overall palatability of the breakfast meal were noted. Liraglutide 1.8 mg and 3.0 mg increased mean postprandial satiety and fullness ratings after the breakfast, and reduced hunger and prospective food consumption, resulting in mean reductions of ~16% *ad libitum* energy intake with liraglutide 1.8 mg (treatment-difference -588 kJ [95% CI -951;-224]; *P*=0.002) and 3.0 mg (-568 kJ [-937;-199]; *P*=0.003) versus placebo. The mean palatability rating of the lunch meal was greater for participants on liraglutide 1.8 mg (treatment-difference 5.9 mm [-1.3;13.2]; *P*=0.11) and 3.0 mg (7.9 mm [0.5;15.3]; *P*=0.04) versus placebo. No statistically significant treatment differences in mean postprandial nausea or well-being ratings were observed.

Conclusion Despite increased palatability ratings of the lunch meal with liraglutide, participants still consumed less than those on placebo, supporting liraglutide's mechanism of action as a satiety signal to reduce appetite and food intake. The reductions in food intake with liraglutide were apparently not confounded by nausea or reduced palatability.

ICAO2013-151

DIET-INDUCED WEIGHT LOSS AND SUBSEQUENT ADDITION OF LIRAGLUTIDE 3.0 MG REDUCES IFG IN OVERWEIGHT/OBESE ADULTS IN THE SCALE™ MAINTENANCE TRIAL

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Objective Impaired fasting glucose (IFG) (FPG 5.6–6.9 mmol/L) is a risk-factor for developing type 2 diabetes and cardiovascular disease. We quantified changes in IFG prevalence (*post-hoc* analysis) from a double-blind, placebo-controlled 56-week randomised trial investigating the effects of liraglutide 3.0 mg on maintenance of diet-induced weight loss (primary endpoint).

Methods Overweight/obese adults (≥18 years, BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities) who lost ≥5% weight after 4–12 week run-in with low-calorie diet (1200–1400 kcal/day) and exercise were randomised to once-daily subcutaneous liraglutide (n=212) or placebo (n=210), plus 500 kcal/day deficit diet and exercise.

Results The full-analysis-set comprised 413 of 422 randomised individuals (age 46.2±11.5 years, BMI 37.9±6.2 kg/m^2 [mean±SD]). During run-in, participants lost 6.3±1.6 kg weight and IFG prevalence decreased from 54% (224/413) to 40% (164/413). At week 56, liraglutide-treated participants lost an additional 5.7 kg from randomisation (Table), whereas placebo-treated participants lost no additional weight (treatment-difference -5.9 kg [95%CI -7.3;-4.4]; *P*<0.0001). Moreover, the proportion of participants with IFG at week 56 was lower for liraglutide (6.3%) than placebo (28.7%; odds-ratio 6.0 [3.1;11.6]; *P*<0.0001). At week 68, after 12 weeks off treatment, the liraglutide group regained ~2 kg lost weight and IFG prevalence increased. Mean weight loss remained greater for liraglutide versus placebo (treatment-difference -4.0 kg [-5.8;-2.2]; *P*<0.0001) but IFG prevalence did not differ (odds-ratio 1.3 [0.78;2.3]; *P*=0.30).

Conclusion Liraglutide decreases IFG prevalence in overweight/obese individuals who have already lost weight by diet and exercise, potentially due to additional weight loss and weight-loss independent mechanisms.

		Liraglutide 3.0 mg	Placebo
Week 0	**IFG (n, %)**	78/207 (38%)	86/206 (42%)
	Weight (kg) (mean±SD)	100.7 ± 20.8	98.9 ± 21.2
Week 56*	**IFG (%)**	6.3%	28.7%
	Weight (kg)#	−5.7	0.16
Week 68*	**IFG (%)**	25.4%	31.0%
	Weight (kg)#	−3.4	0.53

*Last observation carried forward, model estimate

#Change from week 0

Diabetes

ICAO2013-034

BENEFICIAL EFFECT OF THE TAGATOSE CONSUMPTION ON POSTPRANDIAL HYPERGLYCEMIA IN KOREANS: DOUBLE-BLINDED CROSSOVER DESIGNED STUDY

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Objective The present study determined the effect of tagatose supplementation on postprandial hyperglycemia in normal (n=54) and hyperglycemic subjects [n=40, impaired fasting glucose (IFG), and newly diagnosed type 2 diabetes].

Methods In a double-blinded crossover designed study, study subjects were randomly assigned to a sucralose-erythritol drink (the placebo) or to a tagatose-contained drink (the test) with a seven-day interval. Finally, 85 subjects completed the study (normal, n=52; hyperglycemic: n=33). Blood samples were collected at 0, 30, 60 and 120 min after ingestion and analyzed for fasting and postprandial levels of glucose, insulin and C-peptide.

Results Basic anthropometric parameters and lipid files were also measured. Hyperglycemic subjects were basically older and heavier, and showed higher levels of triglyceride, total- and LDL-cholesterols and apoliporpotein AI and B compared with normal subjects. After consuming the tagatose (5g)-contained drink, hyperglycemic subjects had significant reduction in serum levels of glucose at 120 min (p=0.019) and glucose area under curve (AUC) (p=0.017), however which were not observed in normal subjects. When age were matched between the two groups, the glucose response patterns were shown in similar. Additionally, normal subjects who received high-dose tagatose-contained drinks (10g), showed significantly lower levels of insulin at 30 min (p=0.004) and 60 min (p=0.011), insulin AUC (p=0.009), and C-peptide at 30 min (p=0.004), 60 min (p=0.011) and C-peptide AUC (p=0.023).

Conclusion In conclusion, single dietary supplement in a form of the tagatose-contained drink may be beneficial for controlling postprandial glycemic response in Koreans.

ICAO2013-068

EFFECTS OF WHOLE GRAINS AND LEGUMES ON APOA5 -1131C VARIANT IN PATIENTS WITH IMPAIRED FASTING GLUCOSE OR TYPE 2 DIABETES

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Objective The apolipoprotein A5 gene (*APOA5*) -1131T>C polymorphism is associated with mild hypertriglyceridemia in type 2 diabetic subjects and interacts with dietary fat in the determination of triglyceride concentrations. We examined whether a substitution of whole grains and legumes for refined rice in a high carbohydrate diet (about 65% of energy derived from carbohydrate) may modify the effect of this variant on changes in apolipoprotein A-V (apoA-V) and triglyceride concentrations.

Methods We genotyped the *APOA5* -1131T>C in individuals with impaired fasting glucose (IFG) or newly diagnosed type 2 diabetes, who were randomly assigned to either a group ingesting whole grain and legume meals daily or a control group for 12 weeks.

Results After dietary intervention, we observed significant interactions between the *APOA5* -1131T>C polymorphism and carbohydrate sources (whole grains and legumes vs. refined rice) in the determination of mean percent changes in triglyceride and apoA-V (P-interactions <0.001 and =0.038, respectively). In the refined rice group (n=93), the carriers of risk C allele (n=50) showed greater increase in mean percent changes of triglyceride and apoA-V than did noncarriers after adjusted for HOMA-IR (P=0.004 and 0.021, respectively). The whole grain and legume group (n=92), however, showed a decrease in fasting glucose, HOMA-IR, and triglyceride and an increase in apoA-V irrespectively of genotype.

Conclusion Our data showed that the magnitude of the genetic effect of *APOA5* -1131C variant on triglyceride and apoA-V levels was modulated when substituting consumption of whole grains and legumes for refined rice as a carbohydrate source in IFG or diabetic subjects.

Fasting glucose, insulin, free fatty acid, triglyceride, HDL-cholesterol, apolipoprotein A-V, and estimates of daily nutrient intake according to diets and *APOA5* -1131T>C genotype at baseline and 12 weeks

	Whole grains and legumes (n=92)				Refined rice (n=93)			
	TT (n=41)		C allele (n=51)		TT (n=43)		C allele (n=50)	
	Baseline	12wk	Baseline	12wk	Baseline	12wk	Baseline	12wk
Glucose (mg/dL)§	107.9±2.67	97.9±2.12***	107.7±2.83	100.4±2.54***	105.9±2.21	108.8±2.51^{†,e}	110.1±2.39	111.5±2.59^{f}
Insulin (uIU/mL)§	9.96±0.86	8.69±0.65†	9.49±0.75	8.54±0.76**	9.54±0.76	9.65±0.76	9.49±0.62	10.0±0.77
HOMA-IR§	2.61±0.25	2.06±0.16**	2.46±0.22	2.08±0.21**	2.51±0.23	2.60±0.24	2.52±0.18	2.72±0.25^{f}
Free fatty acid (uEq/L)§	564.1±34.8	567.0±29.5	548.9±28.5	583.8±29.9	548.0±30.0	549.8±37.3	535.6±24.4	558.7±31.5
Triglyceride (mg/dL)§	139.8±7.56	123.6±6.85***	186.7±11.4^{a}	173.3±16.8^{**,b}	137.1±11.3	136.3±11.5	170.9±10.7^{c}	218.1±21.7^{***,d,f}
HDL-cholesterol (mg/dL)§	52.3±1.70	54.9±1.94†	48.6±1.37	51.2±1.51*	55.1±2.21	55.9±1.98	48.2±1.88^{c}	49.3±1.93^{d}
ApoA5 (ng/dL)§	225.8±10.2	249.6±14.0†	190.0±9.03^{a}	215.7±9.70**	241.2±11.1	239.5±12.7	194.9±10.2^{c}	223.9±9.92**
Total energy expenditure (kcal/d)	2050.8±43.4	2046.2±42.3	2047.2±49.2	2037.8±45.6	2018.5±44.9	2009.7±41.5	2066.4±36.7	2055.0±34.8
Estimates of daily nutrient intakes								
Energy intake (kcal/d)	2261.8±47.0	2266.0±45.3	2205.2±52.4	2189.4±45.1	2128.6±45.3	2120.3±43.0^{e}	2213.5±39.9	2204.6±38.6
Carbohydrate (%)	64.9±0.93	64.0±0.61	65.4±0.44	64.2±0.59	65.8±0.82	63.4±0.46**	64.6±1.02	64.0±0.56
Protein (%)	17.1±0.41	19.3±0.25***	17.4±0.29	19.4±0.25***	17.4±0.22	17.3±0.20^{e}	17.2±0.37	16.7±0.31^{f}
Fat (%)	21.7±0.59	23.5±0.58*	21.6±0.49	23.3±0.55*	21.2±0.43	21.8±0.50^{e}	21.4±0.61	21.2±0.46^{f}
Crude fiber (g)§	8.86±0.46	10.8±0.58*	10.7±0.64^{a}	11.4±0.79	10.4±0.65	10.6±0.70	10.3±0.71	8.64±0.52^{**,d,f}
PUFA/SFA§	1.59±0.14	1.82±0.12*	1.65±0.13	1.85±0.11*	1.76±0.15	1.73±0.15	1.65±0.14	1.49±0.13^{f}

Means ± S.E. § tested by logarithmic transformation.
^{a}P<0.05 comparison between TT and C allele at whole grains and legumes at baseline.
^{b}P<0.05 comparison between TT and C allele at whole grain treatment at 12wk follow-up.
^{c}P<0.05 comparison between TT and C allele at refined rice at baseline.
^{d}P<0.05 comparison between TT and C allele at refined rice at 12wk follow-up.
^{e}P<0.05 comparison between TT at whole grain and refined rice at 12wk follow-up.
^{f}P<0.05 comparison between C allele at whole grain and refined rice at 12wk follow-up.
$^{\dagger}P$<0.1, $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001 compared with the level at baseline in each group by paired *t*-test.

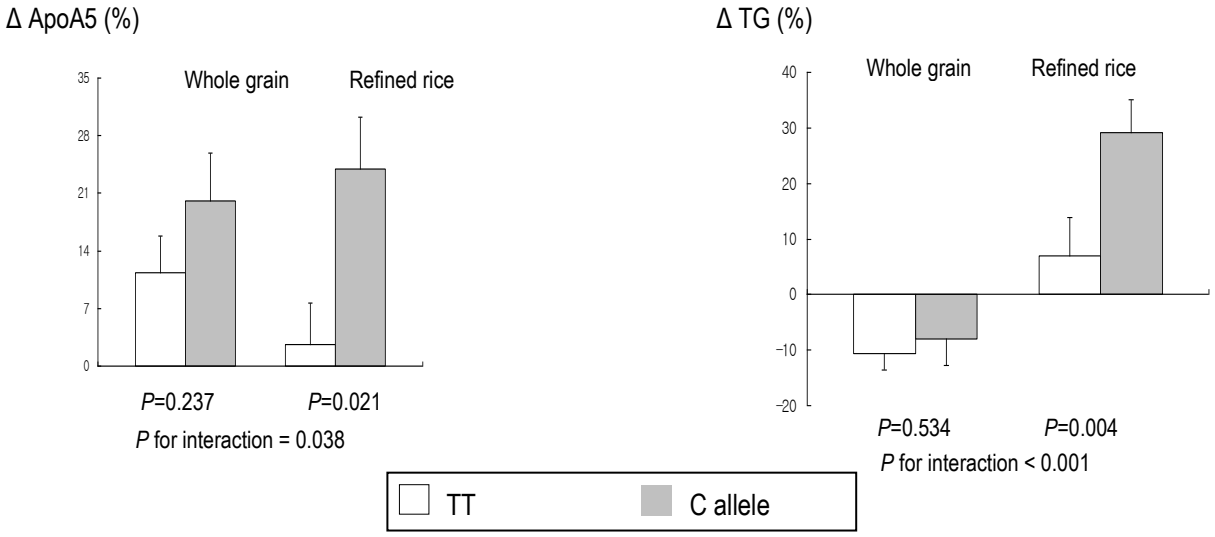

Figure 1. Genotype effect of *APOA5* -1131T>C on mean percent changes in fasting apolipoprotein A-V and triglyceride by whole grains and legumes and refines rice groups at 12 weeks.
Means + SE. *P*-values derived from independent *t*-test after adjusted for change HOMA-IR.

ICAO2013-079

VITAMIN C EFFECT ON SERUM LEVELS OF RESISTIN IN TYPE 2 DIABETES PATIENTS

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Objective Resistin is a cysteine-rich adipose-derived peptide hormone that involvement with obesity and type 2 diabetes mellitus. Resistin accelerates the accumulation of LDL in arteries, increasing the risk of heart disease. In the current research was investigated the effect of oral consumption of vitamin C on serum levels of resistin in patients with type 2 diabetes.

Methods Serum sample obtained from type 2 diabetes patients (n = 80) before and after a short-term consumption of vitamin C (1000 mg for 1 month). The levels of serum glucose, lipid profile, resistin, insulin and hs-CRP were measured by methods of enzymatic, immunoassay and/or high-sensitivity latex agglutination.

Results This investigation showed serum levels of resistin, insulin, total cholesterol, hs-CRP and HOMA-IR index significantly decrease with consumption of vitamin C. However there was no significant difference in levels of glucose, HDL and VLDL after consumption of vitamin C.

Conclusion Results of this research appear which short-term consumption of 1000 mg vitamin C for one month could significantly reduce lipid profile and serum resistin levels in diabetes patients (type 2). Therefore vitamin C can probably decrease the risk of heart disease in these patients.

ICAO2013-081

EFFECT OF CYNARA SCOLYMUS L ON FASTING BLOOD SUGAR OF RAT

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Objective Since ancient times, plants have been an exemplary source of medicine. Iranian literature mentions the use of plants in treatment of various human ailments. In the streptozotocin induced diabetic rats treated separately with diet of dry leaves of cynara Scolymus L.

Methods Administration of 200 mg/kg body weight of diet of Cynara Scolymus L to STZ-diabetic animals daily 3 times for one day brought down fasting blood sugar (FBS) levels while in the untreated group FBS remained at a higher value.

Results The effect of oral administration of dry leaves Cynara Scolymus L on plasma glucose is presented in. The experimentally induced- diabetes increased the level of plasma glucose by 183.1% of control level (Table 1). However, treatment of STZ-diabetic rats with the juices of dry leaves Cynara Scolymus L reduced their plasma glucose levels by 66.8%, compared with the STZ-diabetic group.

Conclusion The objective of the present study was to evaluate the preventative effect of 6 weeks dry leaves Cynara Scolymus L treatment on streptozotocin-diabetic rats. The results of plasma glucose (Table 1) is consistent with the finding other researchers with other sources (Augusti and Sheela (7) and Campos et al. (8) in rats), found a significant decrease in blood sugar level in the Cynara Scolymus L treated STZ-diabetic rats.

Table 1. Effect of cynara Scolymus L on STZ -diabetic rat

NO	Blood sugar (mg /ml)befor STZ	Blood sugar (mg /ml) one week after STZ	Blood sugar (mg /ml)4 weeks after STZ and treat with cynara Scolymus L
1	240	528	450
2	247	460	226
3	250	430	240
4	250	316	167
5	245	583	468
6	203	137	134
7	320	558	450
8	295	585	430
9	225	470	230
10	230	520	270

ICAO2013-087

ELEVATED SERUM FERRITIN LEVEL IS ASSOCIATED WITH THE DEVELOPMENT OF DIABETES IN HEALTHY KOREAN MEN

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Objective Elevated ferritin concentration has been implicated in the etiology of type 2 diabetes. Accumulating evidence, mostly from studies conducted on western populations, has demonstrated a strong association between the elevated ferritin concentrations and the development of type 2 diabetes. In Asian populations, however, the longitudinal studies investigating the association of elevated serum ferritin levels and type 2 diabetes are lacking. In present study, we aimed to determine whether elevated serum ferritin levels are related to the development of type 2 diabetes in healthy Korean men.

Methods This 4 year retrospective longitudinal observational study was conducted at the Asan Medical Center, Seoul, Republic of Korea. The study population consisted of 2,029 men without type 2 diabetes who underwent routine health examination in 2007 (baseline) and 2011 (follow-up). Baseline serum ferritin concentrations were measured by chemiluminescent two-site sandwich immunoassay.

Results During a 4 year period, 186 incident cases of diabetes (9.2 %) were identified. Incident type 2 diabetes increased across the baseline ferritin quartile categories (*P* for trend= 0.003). In multivariate-adjusted model, the relative risk (RR) for the development of type 2 diabetes was significantly higher in highest compared with the lowest ferritin quartile category, even after adjusting for confounding variables (RR=1.60, 95% confidence interval 1.02-2.51, *P* for trend=0.043).

Conclusion These results demonstrate that elevated level of serum ferritin is associated with the development of type 2 diabetes in an Asian population.

ICAO2013-088

HIGHER SERUM BILIRUBIN LEVEL AS A PROTECTIVE FACTOR FOR THE DEVELOPMENT OF DIABETES IN HEALTHY KOREAN MEN

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Objective Bilirubin is a natural product of heme catabolism by heme oxygenase, one of key antioxidant enzymes. Recently, it has been recognized as a substance with potent antioxidant and cytoprotective properties. Several studies have shown a significant negative relationship between serum bilirubin levels and the risk of metabolic disorders, including type 2 diabetes. However, most of the studies have been of a cross-sectional design. We designed this study to investigate the longitudinal effects of baseline serum bilirubin concentrations on the development of type 2 diabetes over a 4-year follow-up period in middle-aged Korean men.

Methods This 4-year retrospective longitudinal observational study was conducted at the Asan Medical Center, Seoul, Republic of Korea. The study population consisted of 5,960 men without type 2 diabetes who underwent routine health examinations in 2007 (baseline) and 2011 (follow-up). Baseline serum bilirubin concentrations were determined by the vanadate oxidation method. The development of type 2 diabetes during a 4 year period was determined.

Results During a 4-year period, 409 incident cases of diabetes (6.9 %) were identified. Incident type 2 diabetes decreased across the baseline bilirubin quartile categories (*P* for trend <0.001). In multivariate-adjusted model, the relative risk for the development of type 2 diabetes was significantly lower in the highest (i.e., 1.30-2.00 mg/dl) than in the lowest bilirubin quartile category (i.e., ≤0.90 mg/dl), even after adjustment for confounding variables including homeostasis model assessment of insulin resistance (relative risk=0.69, 95% confidence interval 0.48-0.99, *P* for trend=0.041).

Conclusion The results indicate that serum total bilirubin level may provide additional information for predicting future development of type 2 diabetes, especially in subjects without chronic liver diseases.

ICAO2013-093

MC4R RS17782313 GENE POLYMORPHISM ALTERS GLYCATED HEMOGLOBIN VALUES INDEPENDENTLY OF ITS EFFECT ON BMI IN JAPANESE

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Objective Type 2 diabetes (T2D) is among the leading public health problems in Japan and glycated hemoglobin can be used to screen the population for T2D. Gene polymorphisms, known to be associated with obesity, may predispose individuals to T2D. Melanocortin 4 receptor (*MC4R) rs17782313* has shown one of the strongest associations with body mass index. We conducted a study to investigate whether *rs17782313* (TT vs TC+CC) was associated with glycated hemoglobin (HbA1c).

Methods We conducted a cross-sectional study including 1179 Japanese adults (437 men: 67.7 ± 10.3 years and 686 women: 68.1 ± 10.4 years). *MC4R rs17782313* was genotyped using fast real time polymerase chain reaction (PCR).

Results TC+CC genotype group showed significantly greater body mass index (BMI) (*P*= 0.041) and HbA1c (*P*= 0.009) than TT genotype group after adjustment for gender, age and, for HbA1c, BMI. Further analysis using linear regression analysis confirmed that the effect of *MC4R rs17782313* (β=0.06; *P*= 0.009) was independent of the effect age, gender, BMI, low density lipoprotein cholesterol (LDL-C), Homeostasis model assessment of insulin resistance (HOMA-IR) and of beta cell function (HOMA- ß). This significant independent association was similarly noticed in obese (β=0.10; *P*= 0.017) and non-obese (β=0.06; *P*= 0.044) subgroups.

Conclusion *MC4R rs17782313*was associated with obesity and could confer a certain susceptibility to T2D that could be independent of its pro-obesity effect.

ICAO2013-109

QUANTITATIVE MEASUREMENT OF HEPATIC STEATOSIS BY CONTROLLED ATTENUATION PARAMETER IS POSITIVELY CORRELATED TO INSULIN RESISTANCE

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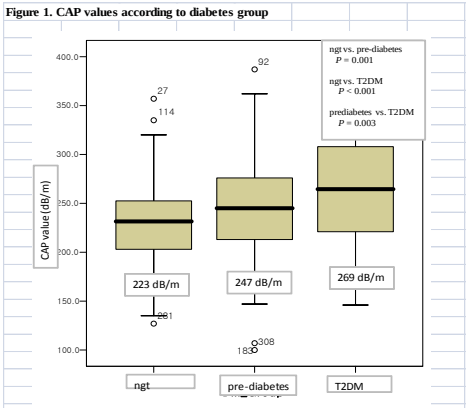
Objective Nonalcoholic fatty liver disease (NAFLD) is highly prevalent in patients with type 2 diabetes mellitus (T2DM) and vice versa. We investigated the interrelationship between amount of hepatic steatosis quantitatively measured by controlled attenuation parameter (CAP) and insulin resistance.

Methods This study included 340 subjects who underwent health check-up evaluation including laboratory tests for insulin resistance and CAP. Correlation between CAP values and biomarkers related to insulin resistance were evaluated. Diagnostic accuracy of CAP for identifying T2DM was calculated by area under the receiver operating characteristic curve (AUROC) and cutoff CAP value was determined by Youden index (sensitivity+specificity-1).

Results Among 340 of study participants (T2DM, n=66; pre-diabetes, n=202; normal glucose tolerance, n=72), mean CAP value was significantly higher in patients with T2DM (269 dB/m) compared to those with pre-diabetes (247 dB/m) or to normal glucose tolerance (223 dB/m) (all P<0.05). CAP value had strong positive correlation with biomarkers related to insulin resistance (fasting glucose, ρ=0.379; fasting insulin, ρ=0.395; C-peptide, ρ=0.402; HbA1c, ρ=0.345; HOMA-IR, ρ=0.407; all P<0.05). CAP value showed an AUROC of 0.653 for identifying T2DM, with 275dB/m as a cutoff for selecting patients with T2DM. CAP value (P=0.013; hazard ratio [HR], 1.011; 95% confidence interval [CI], 1.002-1.016) and age (P=0.001; HR, 1.072; 95% CI, 1.039-1.107) were independent factors associated with T2DM.

Conclusion Our data documented significant cross-sectional correlation between hepatic steatosis quantitatively measured by CAP and biomarkers of insulin resistance. CAP value was an independent factor associated with T2DM.

Figure 1. CAP values according to diabetes group



Patients with T2DM had significantly higher mean CAP values compared to those of pre-diabetes (269 *vs* . 223 dB/m, P <0.001) or normal glucose tolerance (269 *vs*. 247 dB/m, P =0.003). CAP, controlled attenuation parameter; DM, diabetes mellitus; ngt; normal glucose tolerance; T2DM, type 2 diabetes mellitus.

ICAO2013-153

DIETARY INTAKE AND BLOOD GLUCOSE LEVEL OF TYPE 2 DIABETIC PATIENTS ATTENDING A TERTIARY HOSPITAL IN THE NORTHEAST OF THAILAND

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Objective This study aimed to investigate dietary intake and blood glucose level of type 2 diabetic patients (T2DM).

Methods In this cross-sectional study 127 type 2 diabetic patients attending the diabetes clinic of Mahasarakham Hospital, a tertiary Hospital in the Northeast of Thailand, were recruited. A food frequency questionnaire was used to collect data of each food item intakes. The nutrient intakes were obtained from 24-hour dietary recall and analyzed by using the INMUCAL-N version 2 program. Body mass indices, fasting blood glucose values (FBS) and glycosylated hemoglobin values (HbA1c) were extracted from the hospital data.

Results Sixty-six percent of the subjects were females and the mean age was 49.9±6.0 years. The mean duration since the diagnosis of diabetes mellitus was 6.1±3.5 years. Fifty-two percent the subjects were classified as obese (BMI ≥ 25 kg/m^2). The food frequency data revealed that sticky rice was a staple food of the subjects, they consumed fish and vegetable daily, 79 and 68% respectively. Nearly 60% of the subjects consumed high sugar fruits and fried food daily. The median daily energy and protein intakes were 1273 kcal and 63 gm, these were 71% and 118%, respectively, of the Thai recommended daily allowance (RDA). The energy distributions from carbohydrate, protein and fat were 57%, 20% and 23%, respectively. The mean FBS was 160.0 ± 47.6 mg/dl and HbA1c 9.0 ± 1.8 %. The pearson correlation analysis showed that FBS was positive correlation with carbohydrate intake (% of total calories) (p=0.002).

Conclusion Intake of foods which are high in sugar and oil and high carbohydrate contributed in energy intake is a problem of T2DM's consumption. High blood glucose level is also a problem of the patients. Therefore nutrition counseling is recommended, greater emphasis needs to be placed on carbohydrate intake and specific types of food to reduce blood glucose level of the patients.

Ectopic Fat

ICAO2013-053

THE EFFECT OF LIFESTYLE INTERVENTIONS ON ECTOPIC FAT IN OVERWEIGHT ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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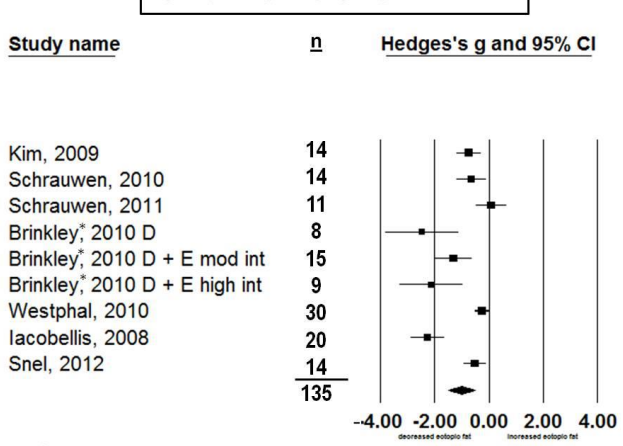
Objective Ectopic fat accumulation seems to play an important role in the pathophysiology of insulin resistance. Therefore, reduction of ectopic fat can be considered an important goal of an intervention program for people with overweight and obesity.
This systematic review and meta-analysis was conducted to summarize the current evidence for different exercise regimes and hypocaloric diet interventions on ectopic fat storage in liver, heart, pancreas and skeletal muscle in overweight and obese adults.

Methods A systematic literature search was performed according to the PRISMA statement for reporting systematic reviews and meta-analyses. The protocol of this review was registered in PROSPERO (CRD 42012002523). Clinical trials in Pubmed, PEDro, and the Cochrane database were searched. Ectopic fat had to be assessed using non-invasive validated methods such as MRs, MRI and CT.
Study eligibility and methodological quality was scored by two independent reviewers with the Cochrane Collaboration's Tool for assessing risk of bias. Data were pooled using random-effects meta-analysis.

Results After screening 31 articles, partly describing multi-arm studies (totaling 1379 patients) fulfilled the inclusion criteria. Effect of lifestyle interventions on ectopic fat storage was analyzed for internal organs (liver, heart and pancreas) and muscle cells (Intra MyoCellular Lipids, IMCL). Using random-effects weights, the standardized mean difference (Hedges's g) of the change in IHL and heart fat was -0.543 [95%CI = -0.672 to -0.415] and -1.004 [95%CI = -1.490 to -0.519] with p< 0.001. Change in IMCL and pancreas fat was less obvious with -0.226 hedges's g [95%CI = -0.374 to -0.079], p=0.003 and -0.552 hedges's g [95%CI = -1.206 to -0.103]; p=0.098.
Heterogeneity analysis showed moderate to high heterogeneity between studies. Subgroup analyses based on different interventions (exercise, diet, diet + exercise) revealed that exercise alone decreases ectopic fat storage. However, the latter was more important when a caloric districted diet was involved.

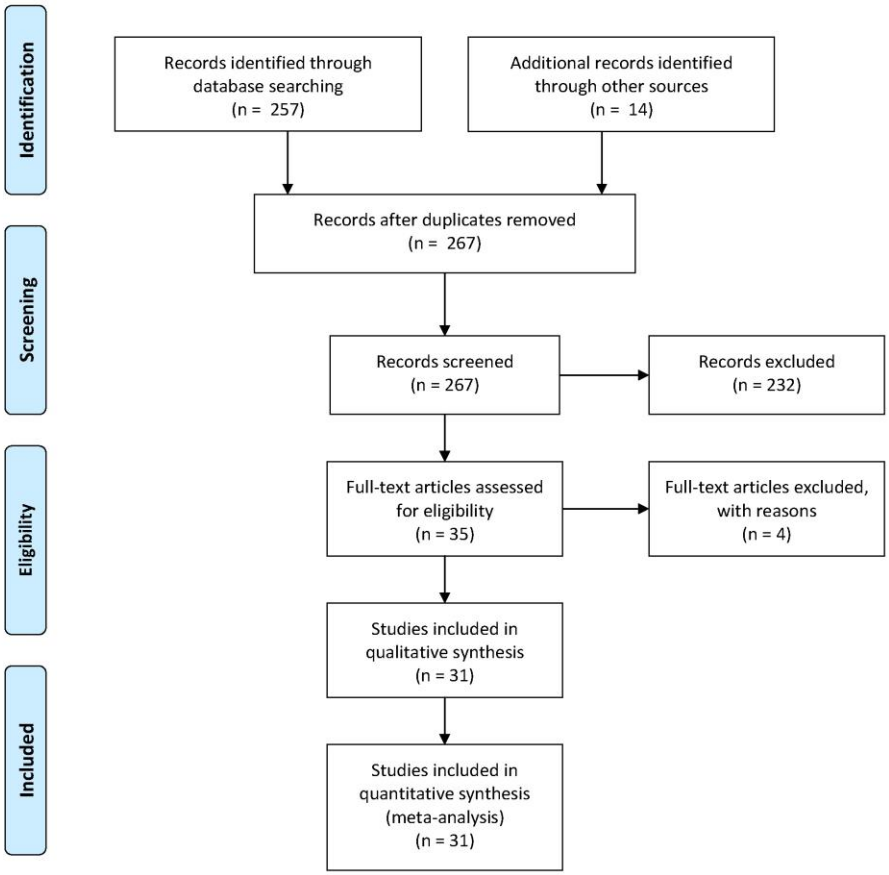
Conclusion This study showed that lifestyle interventions have a beneficial effect on ectopic fat accumulation in the internal organs of overweight and obese adults. The results on IMCL should be interpreted with care, keeping the 'athlete's paradox' in mind.

FOREST PLOT ECTOPIC FAT HEART



* D = diet, E = exercise

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Epidemiology

ICAO2013-084

DIETARY SODIUM INTAKE IS RELATED TO OBESITY AND GLUCOSE CONTROL IN NORMAL KOREAN ADULTS

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Objective Obesity is a complex condition that is influenced by dietary practices and environmental factors. Especially, excessive sodium intake affects hypertension and insulin resistance and is associated with an increased risk for cardiovascular diseases, diabetes, hypertension and premature death. The aim of this study is to investigate the association between dietary sodium intake and obesity in Korean adults.

Methods This study included 5,894 adults (≥ 30 years old) who participated in the Korea National Health and Nutrition Examination survey Ⅴ-1 (KNHANES Ⅴ-1). The subjects were classified into three categories by fasting blood glucose: 1) normal, 2) pre-diabetes and 3) diabetes. The subjects in each category were stratified by dietary sodium intake and indices of obesity were compared.

Results Dietary sodium intake was significantly correlated with waist circumference (WC) in normal ($r=0.073$, $p<0.001$) and pre-diabetic subjects ($r=0.092$, $p=0.007$) and was particularly high in pre-diabetic subjects compared with normal subjects. In multiple logistic regression analysis, the association between dietary sodium intake and WC does not show any association in all categories. On the other hand, dietary sodium intakes and BMI exhibited a significant association (odds ratio 1.239, 95% confidence interval: 1.507–1.453, $p=0.008$). However, these associations were no longer significant after the adjustment for potential confounding factors. Also, the odds ratio for the prevalence of obesity with fasting glucose and HOMA-IR was significantly higher in high sodium intake group compared with low sodium intake group in normal subjects. Furthermore, these associations showed a significant pattern even after adjusting for confounding variables.

Conclusion In conclusion, excessive dietary sodium intake was related to an increased risk of obesity and impaired glucose control in the general Korean adults.

ICAO2013-098

ASSOCIATION OF HIGHER OMEGA-6/OMEGA-3 FATTY ACIDS IN THE DIET WITH HIGHER PREVALENCE OF METABOLIC SYNDROME

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Objective The epidemic of obesity and central obesity over the last two decades, in the middle and high income countries is associated with marked rise in the incidence of metabolic syndrome. The study aims to measure the prevalence of metabolic syndrome (MS) and determine its association with ratio of omega-6/omega-3 fatty acids in the diet.

Methods Cross-sectional surveys were conducted in 20 urban streets in a urban area Trivandrum in South India. Randomly selected subjects (n=1602) aged 25 years and above were evaluated for MS due to presence of central obesity, prehypertension and prediabetes and graded according to omega-6/omega-3 ratio in the diet. Physical examination, sphygmomanometer, questionnaire and blood tests were done.

Results The overall prevalence of MS was 35.1% (n=561) with significantly greater prevalence among men (n=313,39.5% VS n=248,30.6%, P<0.01) compared to women respectively. The prevalence of MS, type 2 diabetes, CAD and hypertension showed a higher rate, in relation to omega-6/omega-3 ratio in the diet. Subgroup analysis showed that subjects eating low omega-6/omega-3 ratio (<5.0) diets had significantly lower prevalence of MS, and related components compared to higher ratio diets, among both sexes. Multivariate logistic regression analysis after adjustment of age showed, that hypertriglyceridemia (odds ratio 0.91 in men, 0.77 in women) was strongly (P<0.01) associated with MS. Hypertension, HDL-C, hyperglycemia and central obesity were weakly associated with MS in both sexes. Hypercholesterolemia was not associated with MS only in women.

Conclusion MS characterized with central obesity, prehypertension and prediabetes has become a public health problem. Higher w-6/w-3 ratio is a major risk factor of MS and CAD. It is possible that a low w-6/w-3 ratio in the diet (<5.0)may be protective against MS and related components of central obesity.

CMR e JOURNAL Official Journal of the International Chair on Cardiometabolic Risk

ICAO2013-140

ABDOMINAL OBESITY IS ASSOCIATED WITH SERUM ORGANOCHLORINE PESTICIDES: A STUDY IN NORTHERN BENIN (WEST AFRICA)

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Objective High pesticide use as observed in certain parts of Africa may be detrimental to health. We examined overall (OVO) and abdominal obesity (ABO) according to serum levels of organochlorine pesticides (OC) in persons living with type-2 diabetes and control subjects.

Methods In a case-control study, 106 diabetic adults were paired with 106 euglycemic subjects by age, gender, ethnic group and residence area. Serum concentrations of four detected OCs were measured in 116 men and 96 women by gas chromatography coupled to mass spectrometry: p,p'-DDT, p,p'-DDE, beta-hexachlorohexane and trans-nonachlor. Three criteria were used for ABO: 1) metabolic syndrome criterion of waist circumference (WC) of 80 cm for men and 94 cm for women; 2) the suggested cut-off for African subjects of 86 cm for men and 92 cm for women; 3) WC/height ratio above 0.5. BMI ≥ 30 defines OVO. Fat mass (FM) based on bioelectrical impedance and Sun formula was considered high when above 0.25 for men and 0.33 for women. Socioeconomic status (SES) was computed based on household assets, education level and occupation.

Results High FM (28.8%) and ABO (60.4%) affect more diabetic than non-diabetic subjects (except for OVO), more women than men, and wealthier than lower SES individuals. When the 3rd tertile of OC level was compared with the 1st tertile, ABO was consistently associated with all four OCs. The association with OVO and high FM was less consistent. According to logistic regression, ABO was associated with a two to fourfold increase in OC levels after adjusting for diabetes status, gender and SES. The WC/H ratio showed the best sensitivity (0.69), specificity (0.54) and area under the curve (0.57) among ABO criteria.

Conclusion Our findings show that high OC exposure as reflected by serum levels is associated with ABO. Knowing that serum levels (ng/g lipids) is a reflection of adipose tissue concentrations, these findings may confirm that ABO is the most adverse pattern of fat storage and may increase the risk of OC-related diseases in highly exposed individuals. Out of the three ABO indicators, WC/height ratio appeared as the most valid in the context of this study.

ICAO2013-161

THE PRESENCE OF METABOLIC SYNDROME DIDN'T SHOW ADDITIVE EFFECT ON CVD RISK AND MORTALITY IN INDIVIDUALS WITH DIABETES

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Objective We examined the separate effect of metabolic syndrome and diabetes on cardiovascular disease (CVD) event risk and mortality. We also evaluated the combined effect of metabolic syndrome and diabetes.

Methods A total 10,038 participants were recruited from the Ansung-Ansan cohort study. Participants were categorized into four groups by presence of metabolic syndrome and diabetes at baseline: The duration of follow-up was 8.0 ± 2.8 years with a total of 71,540 person-years of exposure. After applying exclusion criterion, a total 8,898 subjects were analyzed.

Results 692 of the 8,898 participants developed CVD, and of which 101 CVD deaths occurred. Compared with individuals in the absence of metabolic syndrome and diabetes, subjects who had diabetes alone had increased hazard ratio (1.87, 95% CI 1.38-2.53) for CVD events, and that was no different from HR (1.71, [1.41-2.06]) of subjects with metabolic syndrome only. However, when compared with metabolic syndrome only group, the age, sex, and smoking-adjusted risk of CVD mortality was higher in individuals with diabetes only (HR 2.02 [0.99-4.12]). The presence of metabolic syndrome was not associated with incident CVD and CVD mortality in individuals with diabetes (1.23[0.44-1.68], 0.86 [0.44-1.68], respectively)

Conclusion There was no difference in the risk of CVD events between individuals with diabetes alone and metabolic syndrome alone, whereas CVD mortality was much higher in individuals with diabetes only than in subjects with metabolic syndrome only. In addition, the presence of metabolic syndrome didn't show additive effect on CVD risk and mortality in individuals with diabetes.

Hypertension

ICAO2013-024
MITOCHONDRIAL DYSFUNCTION OF ENDOTHELIAL PROGENITOR CELLS FROM PERIPHERAL BLOOD IN PREGNENCY INDUCED HYPERTENSION

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Objective To explore the functions of endothelial progenitor cells (EPCs) and mitochondrial functions of EPCs from peripheral blood in pregnancy induced hypertension.

Methods Human EPCs were isolated and cultivated from human peripheral blood and characterized. Cell proliferation, migration and in vitro vasculogenesis were assayed using the MTT assay, modified Boyden chamber, and in vitro vasculogenesis detection respectively. The mitochondrial morphology and functions were also observed. The levels of mitochondrial number, mitochondrial morphology and ROS were also assayed using fluorescence PCR, electron microscope fluorescence probe DCFDA (2',7'-Dichlorofluorescein diacetate) respectively.

Results EPCs from peripheral blood of pregnancy induced hypertension had lower EPCs functions of migration and vasculogenesis in vitro compared with control. Mitochondrial functions of EPCs had also changed. Morphological of EPCs mitochondria became smaller and condensed, and some appeared hollow and absent of cristae. Mitochondrial membrane potential and production of intracellular ATP had decreased, as well as accumulation of significant amounts of reactive oxygen species (ROS).

Conclusion The results showed that pregnancy induced hypertension had decreased EPCs adhension, migration and in vitro vasculogenesis. Pregnancy induced hypertension had resulted in an abnormal morphology, a decrease in mitochondrial number and mitochondrial membrane potential and an increase in ROS levels. Our results indicated that mitochondrial dysfunction of EPCs might be responsible for the decreased function of EPCs in pregnancy induced hypertension.

ICAO2013- 086
HIGH FRUCTOSE INDUCES INFLAMMATION ACCOMPANIED BY NLRP3 INFLAMMASOME ACTIVATION

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Objective Consumption of dietary sugar has been linked to obesity, diabetes, and cardiovascular diseases. However, it is unclear which type of simple sugars (glucose or fructose) increases metabolic risks in type 2 diabetes. So, the aim of this study was to investigate the effects of different type and contents of simple sugars on the metabolic parameters and inflammation in a rodent model of type 2 diabetes.

Methods 9 weeks old KK/HlJ male mice were divided into five groups and treated for 21 days: 1) control (CON), 2) moderate glucose (MG, 30%), 3) high glucose (HG, 60%), 4) moderate fructose (MF, 30%), and 5) high fructose (HF, 60%). Indices of glucose control, lipid profiles, inflammatory markers, and components of NLRP3 inflammasome were analyzed.

Results Food intake was not affected by treatments. With HG diet, glucose control was impaired shown as higher fasting blood glucose and lower serum insulin than the other groups. In contrast, dietary fructose showed protective effects against impaired glucose control. After high fructose treatment, lipid profiles such as serum and hepatic triglyceride were exacerbated. Compared with HG diet, HF diet led to the increased expression of apoptosis-associated speck-like protein containing a CARD (ASC), NLR family, pyrin domain containing 3 (NLRP3) and caspase1 (Casp1), which was accompanied by the increased levels of hepatic inflammatory markers (TNF-α and IL-6). However, there were no differences in the level of ASC and NLRP3 between CON and HG group.

Conclusion In conclusion, HF diet worsens lipid profile and inflammation accompanied by NLRP3 inflammasome activation. Taken together, these results have indicated that the high fructose consumption is hazardous to the type 2 diabetes.

ICAO2013-102

INFLAMMATORY MEDIATORS IN CHRONIC HEART FAILURE IN NORTH INDIA

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Objective Recent evidence shows that pro-inflammatory cytokines may be important in the assessment of severity and prognosis in congestive heart failure (CHF). In the present study, we examine the association of cytokines with causes, grade and prognosis of CHF patients.

Methods Of 127 patients with CHF, 11 were excluded and the remaining 116 patients with different aetiologies of CHF, and 250 age and sex matched control subjects, were evaluated in this case study. Severity of disease based on the New York Heart Association (NYHA) standards fell within functional classes II to IV. The diagnosis of HF was based on clinical manifestations as well as on echocardiographic heart enlargement. Cytokines were measured by chemiluminescence. Causes of deaths were assessed based on death certificates.

Results Echocardiographic ejection fraction was 39.1 ± 8.2% (mean±SD) in the study group indicating class II-IV heart failure. Laboratory data showed increase in biomarkers of oxidative stress, IL-6 and TNF-alpha among HF patients with low ejection fraction compared to those with normal ejection fraction and compared to healthy subjects. TNF-alpha and IL-6, showed significant increase among patients with CHF due to ischaemic heart disease and cardiomyopathy compared to levels among CHF patients with valvular heart disease and hypertensive heart diseases. The levels of the cytokines were significantly higher among patients with class III and IV heart failure and those who died, compared to patients with class II heart failure. Of 116 patients, 20(17.2%) died during a follow up of two years, and the deaths were mainly among NYHA class III and IV patients in which the cause of CHF was CAD (10.9%) and cardiomyopathy (6.9%) which had greater levels of cytokines. Multivariate logistic regression analysis showed that class III and IV heart failure, higher IL-6 and TNF-alpha, and CAD were strongly associated with deaths whereas cardiomyopathy and duration of heart failure were weakly associated with deaths due to CHF. Hypertension was not associated with deaths.

Conclusion The findings indicated that pro-inflammatory cytokines may be important indicators of causes, severity of CHF and prognosis among these patients.

Insulin Resistance

ICAO2013-026
IMMOBILIZATION STRESS EXACERBATES INSULIN RESISTANCE AND ENDOTHELIAL DYSFUNCTION: INVOLVEMENT OF ROCK ACTIVITY AND INFLAMMATION

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Objective Psychological stress may contribute to the development of atherosclerosis and insulin resistance. However, its mechanism is poorly understood. We studied if stress induces insulin resistance and endothelial dysfunction, and investigated the involvement of ROCK activity and inflammation in this study.

Methods Immobilization stress (IS) was applied (2 hr/d) for 14 d to male 8-wk (YI2O: before DM phenotype) and 21-wk (EI2O: DM phenotype) OLETF rats, whereas control groups comprised of rats without IS with same age (YCO and ECO, respectively; n=7~10 for each group). After scarifying, NO release by acetylcholine 10^{-5}nM were directly measured aorta's inner surface, using electrochemical NO microsensor. Also, plasma was used for insulin and several metabolic indices. Western blot analysis and RT-qPCR were performed at rat tissues and HUVEC endothelial cell line.

Results Systolic blood pressure and metabolic indices was significantly not changed by IS, compared with control groups. NO release of aorta by acetylcholine and acetylcholine-induced vasorelaxation were decreased by 14d-IS compared with control, suggesting that IS induced endothelial dysfunction. 14d-IS increased plasma insulin (342.5±0.3 vs 496±1.6 pg/ml) and HOMA-IR (3.1±0.2 vs 4.7±0.5 mmol/L X μIU/ml) in 8-wk OLETF rats, indicating that IS could induce insulin-resistance. To investigate its mechanism, western blot analysis in thoracic aorta was performed. As a result, 14d-IS increased expression of Rho-associated kinase-1 and p22phox subunit of NAD(P)H oxidase. Next, to confirm whether IS induced the activation of MAPK and eNOS, HUVEC cell were treated insulin and corticotropin-releasing hormone (CRH). eNOS phosphorylation at Ser1177 was increased by treatment with insulin (2 nM) in HUVEC cells, but this was blocked by CRH (100 nM). On the contrary, an increase in ERK phosphorylation by insulin was further enhanced by CRH pretreatment in HUVEC cells. CRH also induced translocation of NF-κB subunit p65 into nuclear fraction in monocyte cell line U937 cells.

Conclusion Immobilization stress exacerbates insulin resistance and endothelial dysfunction in a prediabetic animal model at least partly via inhibition of insulin-mediated eNOS activation and via enhancement of inflammation through ERK pathway and NF-κB activation by CRH.

ICAO2013-174

SERUM FERRITIN LEVEL IS AN INDEPENDENT DETERMINING FACTOR OF INSULIN RESISTANCE IN NON-DIABETIC MEN AGED 30 – 69 YEARS

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Objective We investigated the associated factor of serum ferritin in the Korean population with Korean National Health and Nutrition Examination Surveys.

Methods Adults aged 30 – 69 years without anemia were selected for the analysis. Fat mass was measured by dual-energy X-ray absorptiometry and nutritional information was collected by 24-h recall. Insulin resistance and beta-cell function was calculated from homeostatic model assessment.

Results 6,256 men and 8,003 women were included the study. Among them, 9.8 (standard error [SE] 0.4) % of men and 6.8 (SE 0.4) % of women had diabetes mellitus (DM) and serum ferritin level was higher in DM patients compared to non-DM subjects both in men and women (P <0.001). Serum ferritin was significantly associated with insulin resistance (age and body mass index adjusted P <0.001) in men, but not in women. It was also associated total body fat (P = 0.009), triglyceride level (P <0.001), alanine aminotransferase (ALT) (P <0.001) and leukocyte count (P <0.001), but not with iron or fat intake. Multivariate analysis showed that serum ferritin level was an independent determining factor of insulin resistance even after adjusting body fat, ALT, triglyceride and leukocyte count (β = 0.027, P = 0.027). Beta cell function was not associated with ferritin level both in men and women.

Conclusion Elevated serum ferritin was a risk factor of DM via increasing insulin resistance rather than affecting beta-cell function. Serum ferritin level was an independent determining factor of insulin resistance even after adjusting body fat or systemic inflammation in men.

Determining factor of insulin resistance (HOMA-IR) in men without diabetes mellitus

Model	β*	*P**
Ferritin (unadjusted)	0.106	<0.001
Ferritin	0.060	<0.001
BMI	1.567	<0.001
Age	–	0.633
Ferritin	0.031	0.002
BMI	1.359	<0.001
ALT	0.149	<0.001
Age	–	0.184
Ferritin	0.030	0.003
BMI	1.340	<0.001
ALT	0.148	<0.001
WBC	0.069	0.005
Age	–	0.144
Ferritin	0.027	0.007
BMI	1.321	<0.001
ALT	0.144	<0.001
WBC	0.057	0.024
Hb	0.273	0.016
Age	–	0.062
Ferritin	0.021	0.027
BMI	1.237	<0.001
ALT	0.121	<0.001
WBC	0.027	0.290
Triglyceride	0.112	<0.001
Age	–	0.495
Ferritin	0.048	<0.001
Total body fat mass†	0.522	<0.001
Age	–	0.108
Ferritin	0.059	<0.001
Fat percent of total body†	0.627	<0.001
Age	–	0.423

* Multi-variate linear regression analysis
Measured by dual-energy X-ray absorptiometry
BMI, body mass index; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance

ICAO2013-177

CONTRIBUTION OF IGFBP-2 TO THE INSULIN SENSITIZATION IMPACT OF ADIPOSE TISSUE LOSS INDUCED BY LIFESTYLE MODIFICATIONS

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Fac Pharmacy, Université Laval, Québec, QC, Canada[1], Fac Medicine, Université Laval, Québec, QC, Canada[2], Cardiology, Quebec Heart and Lung Research Institute, QUébec, QC, Canada[3], Lipid Research Center, CHUL-CHU, Québec, QC, Canada[4]

Objective The insulin-like growth factor (IGF) binding protein 2 (IGFBP-2) is a 36 kDa circulating protein that modulates insulin sensitivity and adipose tissue accumulation. We recently demonstrated that bariatric surgery robustly increases IGFBP-2 levels in obese humans. The present study was aimed at evaluating the impact of a lifestyle modification program (exercise and healthy eating) on IGFBP-2 levels, and whether the extent of these changes modified the cardiometabolic response to such program.

Methods Plasma IGFBP-2 was quantified by ELISA in lean, overweight and obese men before and after 3 years following the onset of a lifestyle modification program (SYNERGIE study), which consisted of nutritional counseling combined with a physical activity program (160 min/week of moderate intensity endurance exercise) designed to elicit a 500 kcal daily energy deficit during the first year, followed by adjustment during the next two years to favor weight maintenance.

Results As expected, the lifestyle intervention program induced significant reductions in body weight, fat mass, triglyceridemia, and fasting glycemia, while promoting an increase in HDL-cholesterol levels, insulin sensitivity and IGFBP-2 plasma levels (+40%, $p < 0.0001$). Changes in IGFBP-2 concentrations were significantly associated with changes in fat mass, triglyceridemia, glucose tolerance during an OGTT, fasting insulin and the HOMA index. Multivariate analysis indicated that changes in circulating IGFBP-2 were independent predictors of the changes in HOMA index (24%, p<0,0001), log cholesterol (15%, p<0,0001) and log triglycerides (4%, p=0,0480).

Conclusion The present findings suggest that an increase in circulating IGFBP-2 triggered by a lifestyle-induced negative energy balance could contribute, at least in part, to the improvements in glucose and lipid metabolism observed in response to such intervention.

Study funded by CIHR

Lipids/Lipoproteins

ICAO2013-043
TREATMENT OF CADMIUM CAUSED HIGH-DENSITY LIPOPROTEIN (HDL) MODIFICATION AND SEVERE METABOLIC TOXICITY IN ZEBRAFISH

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Objective Although neurotoxicity of cadmium is well known, there has been no report to elucidate cadmium toxicity in lipid metabolism. This study designed to elucidate toxicity of cadmium in lipoprotein metabolism.

Methods Cadmium was treated high-density lipoprotein (HDL) and zebrafish consumed cadmium (final 24 μM) with normal diet (ND) or high cholesterol diet (HCD) for 4 weeks.

Results Treatment of cadmium caused more acceleration of low-density lipoprotein (LDL) uptake into macrophage and premature dermal cell senescence. Microinjection of cadmium into zebrafish embryo attenuated embryo development with higher mortality (up to 23% more embryo death). Four weeks consumption cadmium either containing normal diet (ND) and high cholesterol diet (HCD) resulted (final 24μM) 40% and 65% increase of TC and TG, respectively with hepatic inflammation. Serum glucose was more elevated 15% compared with HCD alone control.

Conclusion In conclusion, cadmium exposure caused modification of HDL and elevation of serum lipid profile to result fatty liver change. (Kim HH and Kim JY are co-first authors.)

ICAO2013-046

KIMCHI AND ITS INGREDIENTS ALLEVIATE ENDOPLASMIC RETICULUM STRESS IN THE LIVER OF APOE DEFICIENT MICE FED A WESTERN-TYPE

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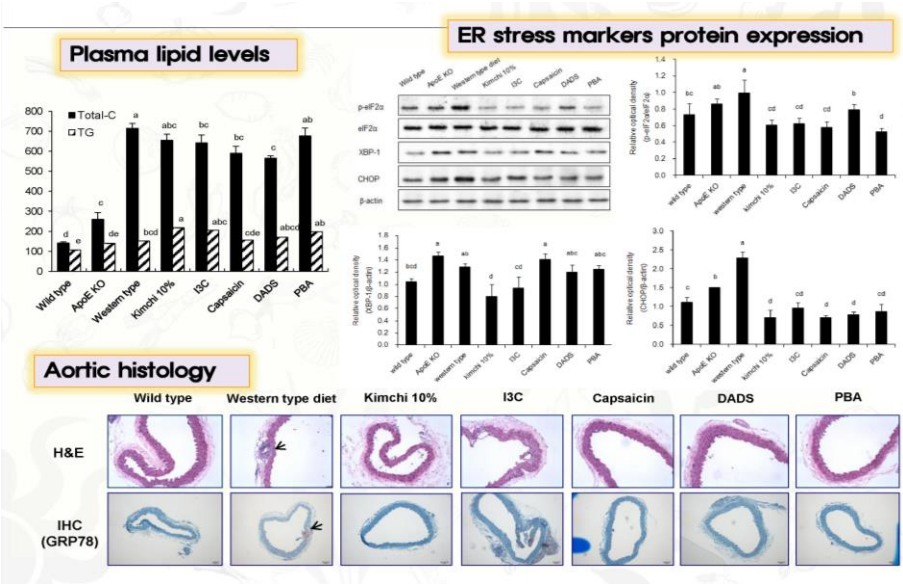
Objective Oxidized low-density lipoproteins (oxLDLs) trigger various biological responses potentially involved in atherogenesis. Disturbing endoplasmic reticulum (ER) function results in ER stress and unfolded protein response, which tends to restore ER homeostasis but switches to apoptosis when ER stress is prolonged. This study evaluated the function of kimchi and its ingredients and investigated its antiatherosclerotic effects in animal models.

Methods ApoE(-/-) mice received a western-type diet to accelerate atherosclerosis. A subset of mice from each group was supplemented with capsaicin for 12 weeks. At 18 weeks of age, lipid levels, markers of ER stress, lipid accumulation were analyzed in liver and aorta. Kimchi (10% freeze dried), indole-3-carbinol (0.05%), Capsaicin(0.015%), and dially disulfide (0.1%) was administrated to apolipoprotein E knockout (apoE-/-) mice fed western-type diet (42% fat, 20% sucrose) for 12 weeks to investigate antiatherosclerotic effects and elucidate its molecular mechanisms.

Results AopE(-/-) mice fed a western -type diet were significantly increased lipid levels, markers of ER stress and lipid accumulation in aorta and liver compared with control mice fed a normal diet. Administration of Kimchi and its ingredients reduced total cholesterol and triglyceride levels in the plasma and liver of apoE(-/-) mice. Furthermore, capsaicin and dially disulfide significantly inhibited expression of ER stress markers(p-eIF2a, XBP-1, CHOP) in the liver of apoE(-/-) and subsequently attenuated the development of atherosclerosis.

Conclusion Kimchi and its ingredients improved lipid metabolic disorders by attenuating ER stress, suggesting that it has potential as an antiatherosclerotic agent for the treatment of atherosclerosis.



ICAO2013-064

CARRIAGE OF THE HOMOZYGOUS GENOTYPE OF V279F WITHIN THE GENE ENCODING LP-PLA2 LEADS TO CHANGE INTERMEDIATE METABOLITES

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Objective Identifying the difference of plasma metabolic profiling between *Lp-PLA*$_2$ 279VV and 279FF in individuals without metabolic syndrome (MS) can significantly contribute to the elucidation of novel Lp-PLA$_2$ activity in normal physiological process.

Methods Non-MS individuals with 279FF (n=36) and age-, sex- and BMI-matched VV subjects (n=36) were included. Plasma metabolomics profiling was analyzed with ultraperformance liquid chromatography coupled to a linear quadrupole ion trap-orbitrap mass spectrometer (UPLC-LTQ-Orbitrap MS).

Results FF subjects showed no appreciable enzyme activity. No significant differences between VV and FF subjects were observed in serum lipid profiles and hs-CRP, plasma ox-LDL, MDA, and urinary 8-epi-PGF$_{2\alpha}$. FF subjects showed lower intensities of lysophosphatidylcholine (lysoPC) (16:0) (P=0.003) and oleamide (P<0.001), and higher L-tryptophan (P=0.016) than VV subjects. Lp-PLA$_2$ activity correlated positively with lysoPC (16:0) and lysoPC (18:0), and negatively with PC (16:0/22:6) and L-tryptophan in VV subjects. Furthermore, in VV subjects lysoPC (16:0) and lysoPC (18:0) negatively correlated with PCs containing 14:0/20:2, 14:0/22:4, and 16:0/22:6, respectively. However, no significant association between lysoPCs and PCs was found in FF subjects. Oleamide strongly correlated positively with lysoPCs and negatively with PCs in VV subjects, whereas this relation of oleamide with lysoPCs and PCs was weaker in FF subjects.

Conclusion This study indicates that natural absence of plasma Lp-PLA$_2$ activity, due to carriage of the *Lp-PLA*$_2$ 279FF genotype, may reduce the generation of lysoPC (16:0) and oleamide and enhance plasma tryptophan in normal physiological process.

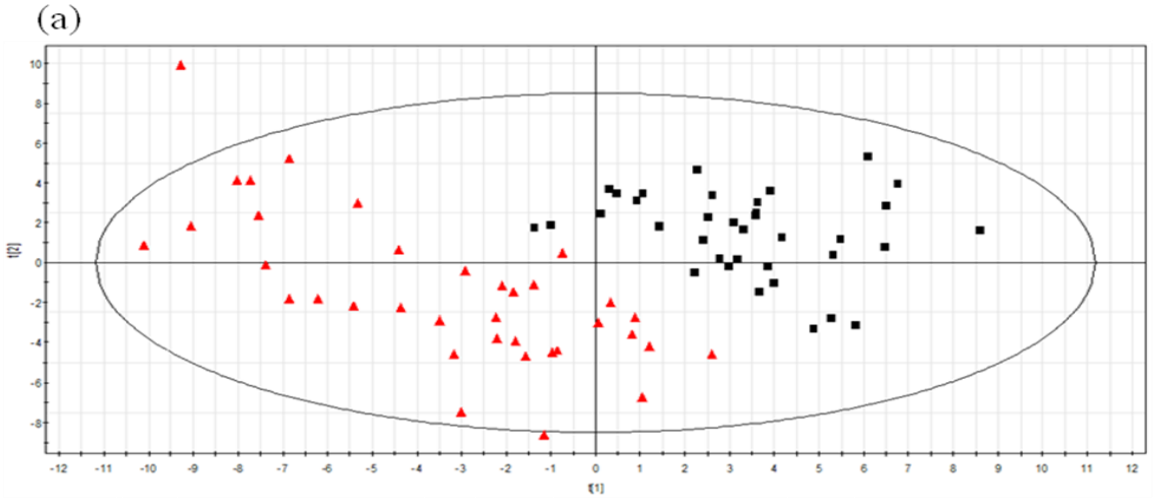
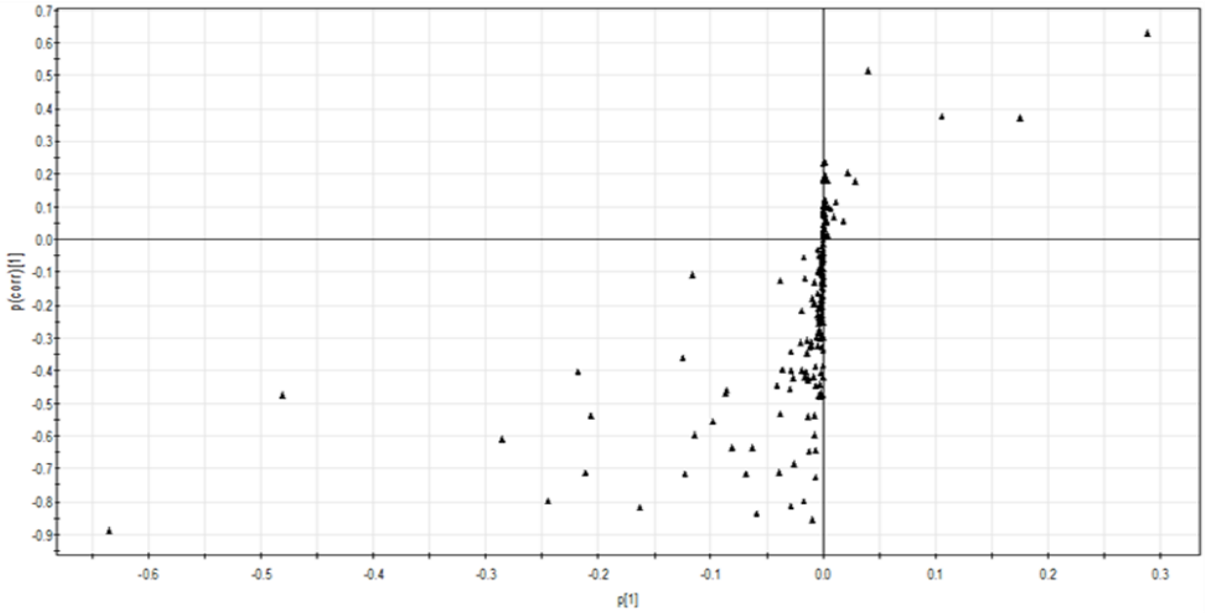


Fig 1. (a) Score plots from partial least-squares discriminant analysis (PLS-DA) models classifying subjects with *Lp-PLA*$_2$ 279VV (*filled triangle*) and 279FF (*filled square*). (b) *S*-plots for covariance [*p*] and reliability correlation [*p*(corr)] from PLS-DA models.

(b)


p(corr)[1]
p[1]
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-0.6
-0.5
-0.4
-0.3
-0.2
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ICAO2013-065

ASSOCIATION OF POLYMORPHISMS IN FADS GENE WITH CHANGES IN SERUM PHOSPHOLIPID POLYUNSATURATED FATTY ACIDS AND OXIDATIVE STRESS MARKERS

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Objective To investigate the association of *FADS* gene polymorphisms with age-related changes in polyunsaturated fatty acids (PUFAs) in serum phospholipids and oxidative stress markers.

Methods We genotyped 122 nonobese men aged 35–59 years without any known diseases at baseline for rs174537 near *FADS1* (*FEN1* rs174537G>T), *FADS2* (rs174575, rs2727270), and *FADS3* (rs1000778), and followed them for 3 years.

Results Among the four SNPs, the minor variants of rs174537 and rs2727270 were significantly associated with lower concentrations of long-chain PUFAs. However, rs174537G>T showed stronger association. At baseline, men with the rs174537T allele had lower arachidonic acid (AA) and AA/linoleic acid (LA), and higher interleukin-6 (IL-6) levels than rs174537GG counterparts. After 3 years, rs174537GG men had significantly increased AA (P=0.022), AA/dihomo-γ-linolenic acid (DGLA) (P=0.007), docosapentaenoic acid (DPA), LDL-cholesterol, and oxidized LDL (ox-LDL); but decreased eicosatrienoic acid. The rs174537T group showed significantly increased γ-linolenic acid and ox-LDL; and decreased eicosadienoic acid, eicosapentaenoic acid (EPA)/α-linolenic acid (ALA), and IL-6. After 3 years, the rs174537T group had lower AA (P<0.001), AA/DGLA (P=0.019), EPA, DPA, EPA/ALA, and urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) (P=0.011) than rs174537GG. Changes in AA (P=0.001), AA/DGLA (P=0.017), EPA, DPA, EPA/ALA, and urinary 8-epi-$PGF_{2\alpha}$ (P<0.001) were significantly different between the groups after adjusting for baseline values. Overall, changes in AA positively correlated with changes in urinary 8-epi-$PGF_{2\alpha}$ (r=0.249, P=0.007), plasma ox-LDL (r=0.199, P=0.045), and serum IL-6 (r=0.289, P=0.004).

Conclusion Our data show that FADS polymorphisms can affect age-associated changes in serum phospholipid long-chain PUFAs, △5-desaturase activity, and oxidative stress in middle-aged nonobese men. In particular, the rs174537T allele did not show the age-associated increases in AA and △5-desaturase activity seen with the rs174537GG genotype.

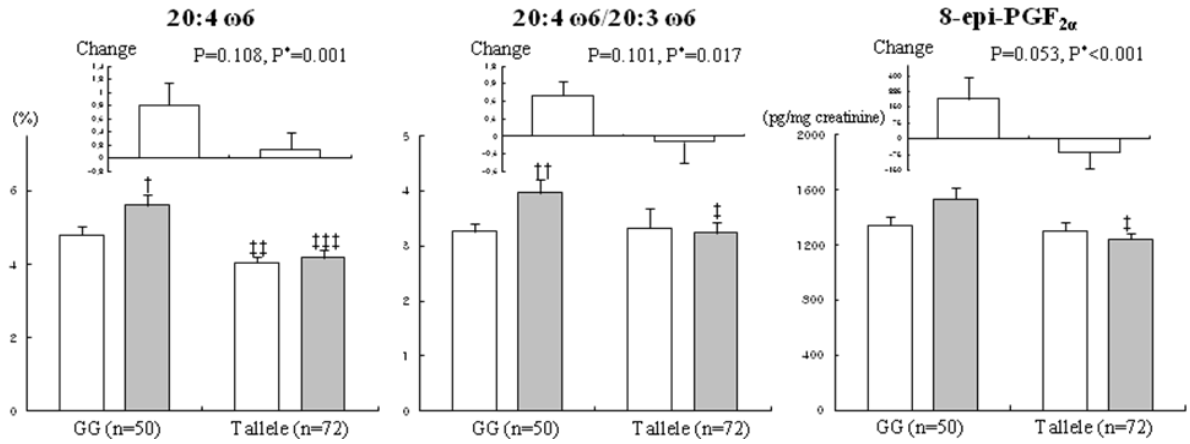

Figure1. Serum phospholipid arachidonic acid (AA, 20:4 ω6), the ratio of 20:4 ω6/20:3 ω6 and urinary levels of 8-epi-$PGF_{2\alpha}$ according to *FEN1* rs174537 G>T in men at baseline (☐) and 3-year follow-up (■)

Means±S.E.; Changes are differences between baseline and 3 years.; †p<0.05, ††p<0.01, baseline vs 3 years, tested by paired t-test.; ‡p<0.05, ‡‡p<0.01, and ‡‡‡p<0.001 GG vs T allele group, tested by independent t-test.; P*: after adjustment for baseline value.

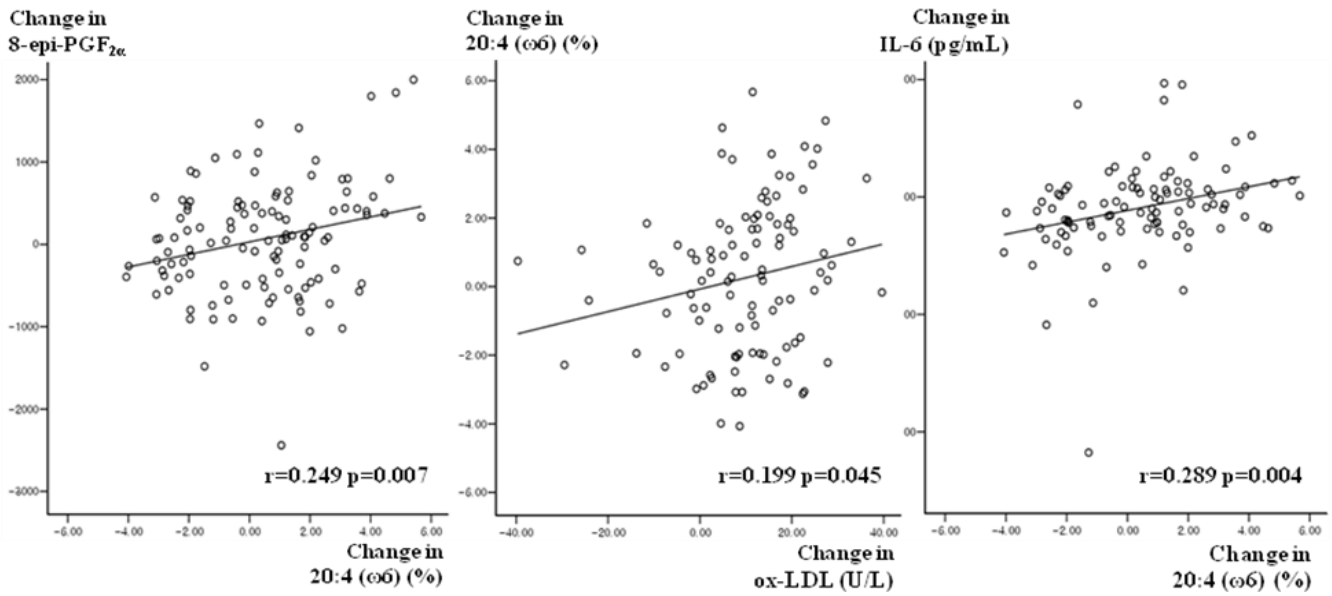

Figure 2. Relation of changes in serum phospholipid arachidonic acid with changes in oxidized LDL, urinary 8-epi-$PGF_{2\alpha}$ and serum IL-6 in all male subjects

Changes are differences between baseline and 3 years.

ICAO2013-066

ASSOCIATION OF AGE-RELATED CHANGES IN CIRCULATING INTERMEDIARY LIPID METABOLITES, INFLAMMATORY AND OXIDATIVE STRESS MARKERS, AND ARTERIAL STIFFNESS IN MIDDLE-AGED MEN

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Objective The relationships between age-related changes in circulating endogenous metabolites, inflammatory and oxidative stress markers, and arterial stiffness in 57 middle-aged (34–55 years), nonobese men were studied over the course of 3 years.

Methods Arterial stiffness was measured using brachial-ankle pulse wave velocities (ba-PWV). Plasma metabolomic profiling was performed using ultra-performance liquid chromatography and quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF MS).

Results After 3 years, decreased HDL-cholesterol and increased malondialdehyde (MDA) and ox-LDL levels were observed. Among 15 identified lipids, lysoPCs (C16:0, C18:0, C18:2, C20:4, and C20:5) and linoleyl carnitine were the major plasma metabolites that contributed to the age-related differences. LysoPC16:0 (variable importance in the projection [VIP] value: 6.2029) was found the most important plasma metabolite for evaluating these changes. Changes in lysoPC16:0 levels positively correlated with the changes in 8-epi-$PGF_{2\alpha}$ (r=0.608), MDA (r=0.413), high-sensitivity C-reactive protein (r=0.509), IL-6 (r=0.497), and ba-PWV (r=0.283) levels. ba-PWV levels positively correlated with the changes in waist-to-hip ratios (WHR), inflammatory and oxidative stress markers. In a subgroup analysis of subjects with decreased ba-PWVs vs. increased ba-PWVs, changes in WHR and levels of lysoPC16:0, ba-PWV, IL-6, 8-epi-$PGF_{2\alpha}$, MDA, and P-selectin were significantly different.

Conclusion Our results suggest that age-related increases in lysoPC16:0 may contribute to lipid peroxidation, thereby, activating proinflammatory phenotypes, and arterial stiffness.

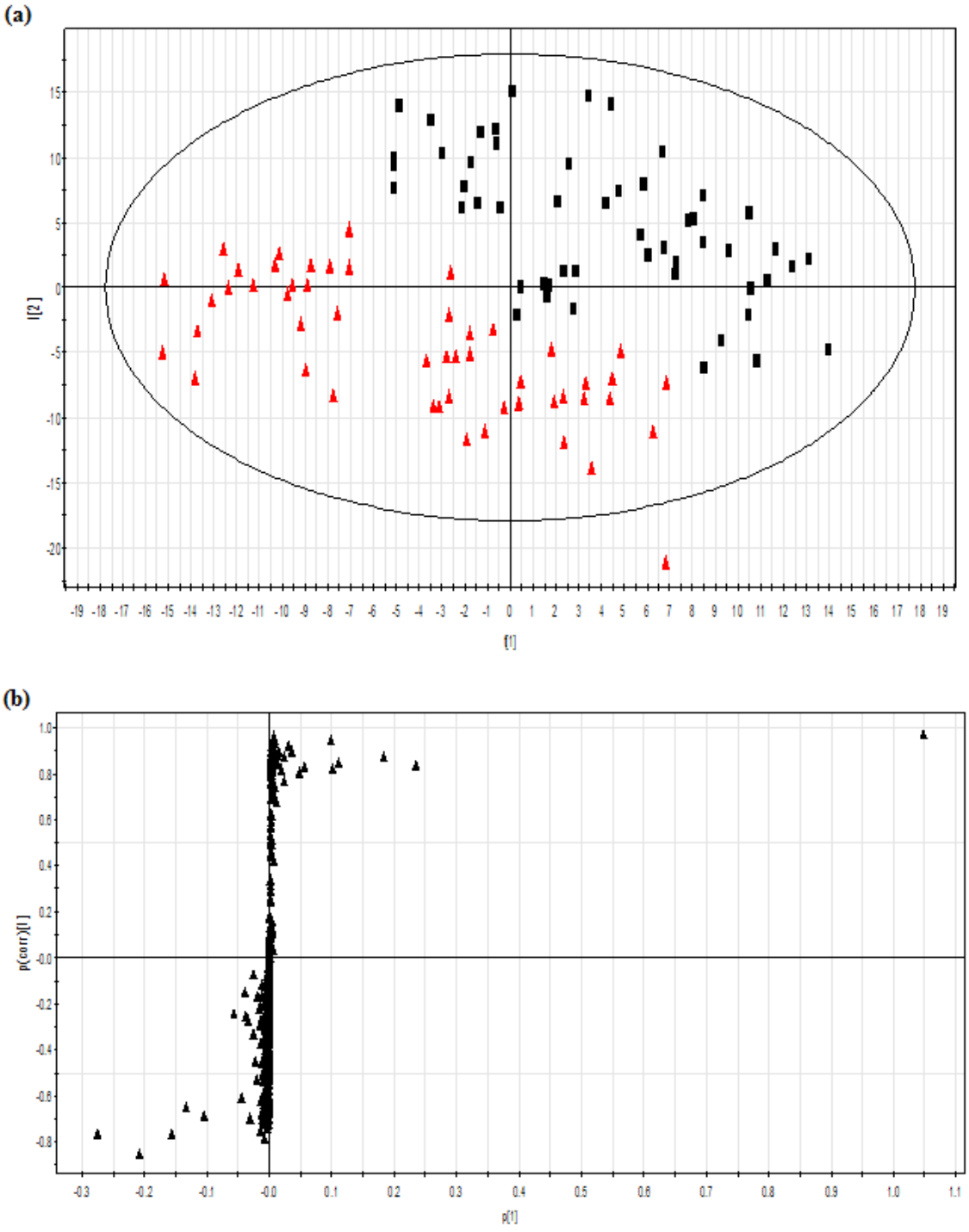

Figure 1. (a) Score plots from PLS-DA models classifying healthy men at baseline (■) and at the 3–year follow-up (▲). (b) S-plot for covariance [p] and reliability correlation [p(corr)] from PLS-DA models.

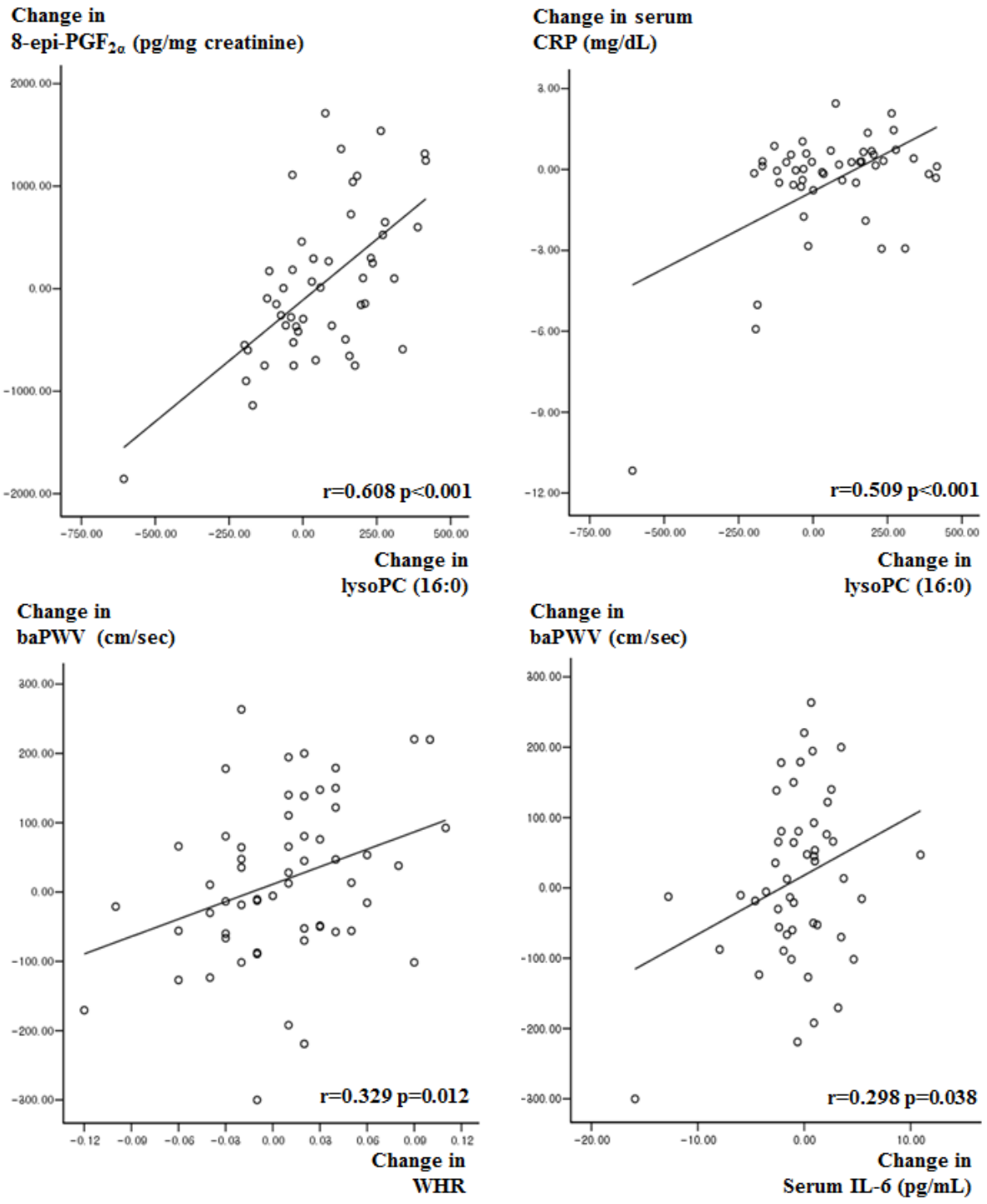

Figure 2. Relationship of the changes in lysoPC(16:0) levels, WHR, and IL-6 with the changes in 8-epi-$PGF_{2\alpha}$, CRP and ba-PWV in healthy men after 3 years. Tested by *Pearson* correlation analysis. r: correlation coefficient.

ICAO2013-080

THE EFFECT OF ALLIUM LATIFOLIUM ON THE SERUM LIPOPROTEINS IN HYPERLIPIDEMIC RATS

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Objective *Allium latifolium* has polyphenolic compounds with power antioxidant properties which reduce lipid peroxidation and serum lipids. Phosphatidate phosphohydrolase (PAP) is a key enzyme in controlling the synthesis of glycerophospholipids. Therefore, the aim of this study was to determine the effect of the hydroalcoholic extract of *Allium latifolium* on the liver PAP, liver triglyceride (TG) and cholesterol (Chol) content, and plasma lipoproteins in hyperlipidemic rats.

Methods 40 Male rats were randomly divided into 8 experimental groups. Group I, normal control rats which received standard diet, group II received cholesterol and oil diet without treatment, group III the rats which received cholesterol and oil plus 150 mg/kg bw *Allium latifolium* extract, Group IV the rats which received cholesterol and oil diet plus 300 mg/kg bw *Allium latifolium* extract, and group V were the rats which received cholesterol and oil diet plus 30 mg/kg bw gemfibrozyl. At the end of the study, liver PAP activity, liver TG and Chol, and serum lipoprotein levels were determined. For statistical analysis of the data, group means were analyzed with one way ANOVA followed by Tukey's test for multiple comparisons.

Results In group II, liver PAP activity showed a significant change ($p < 0.05$) compared to other groups. In groups III and IV(the rats which received *Allium latifolium* extract), the liver Chol and TG, serum HDL-C, TG, total Chol, and VLDL concentrations showed a significant reduction ($p < 0.05$) compared to group II (the rats without treatment). In group IV, serum total Chol indicated a significant elevation ($p < 0.05$) with respect to group III.

Conclusion The consumption of *Allium latifolium* in the low dose can reduce the side effects of hyperlipidemia such as elevated serum Chol and TG. *Allium latifolium* not only can decrease liver PAP and lipid peroxidation but also it can reduce the risk of fatty liver in hyperlipidemic diets.

ICAO2013-094

RECONSTITUTED HIGH DENSITY LIPOPROTEIN MODULATES NEOINTIMAL HYPERPLASIA VIA SMALL HEAT SHOCK PROTEINS IN BALLOON-INJURED RAT CAROTID ARTERY

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Division of Cardiology, SBRI, Samsung Medical Center, Seoul, Korea, Rep.[1], Protein Research Lab, Green Cross Corp., Yongin, Gyeonggi Do, Korea, Rep.[2]

Objective Maintaining low level of low density lipoprotein (LDL) and high level of high density lipoprotein (HDL) in plasma is the most important factor in the prevention of atherosclerosis. HDL therapy can be beneficial in the acute coronary syndrome patients. We tried to investigate the inhibitory effects of reconstituted HDL (rHDL) on restenosis and its mechanism of action using balloon injury rat model.

Methods rHDL was prepared with plasma-derived apoA-I and soybean PC by a molar ratio of 1 to 150. Sprague-Dowley (SD) rats at 6 weeks of age were maintained until weight is reach to 400~450g. To induce neointima formation, the right carotid artery of male SD rat (n=10) was exposed, inserted with a 2F Fogarty catheter in an isolated arterial segment, and then the endothelium was denuded by moving the catheter back and forth 3-4 times. Administration of rHDL was started 4 hr before surgery and continued once a day for two consecutive days after carotid injury. At day 4, or two and four weeks later, injured carotid arteries isolated were stained with H&E and analyzed to assess neointima formation.

Results While there was no significant difference in medial area, intima to media ratios was 35% lower in 80 mg/kg rHDL treated group (p=0.034) compared to the injury only group. Biochemical analysis confirmed that rHDL significantly reduced proliferation of smooth muscle cells and macrophages but it induced proliferation of endothelial cells. Expression of HIF1a and HO1 was reversely regulated by rHDL infusion. In addition, strong CD68 and CD18 signals caused by balloon injury are dramatically diminished by rHDL treatment. Furthermore, MMP9 but not MMP2 induction was also significantly reduced by rHDL treatment.

Conclusion rHDL effectively stabilized restenosis by reducing monocyte infiltration, smooth muscle cell proliferation, and increasing the endothelial cell proliferation. HIF1a and HO1 might play major regulatory roles on progression of restenosis in balloon-injured rat carotid artery.

ICAO2013-118

INCORPORATION OF TRANSFATTY ACID IN HDL CAUSE LOSS OF ANTI-OXIDANT AND ANTI-INFLAMMATORY ACTIVITY IN ZEBRAFISH

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Objective Epidemiologic studies have demonstrated that trans fatty acid is strongly associated with the risk of cardiovascular disease and type 2 diabetes. Apolipoprotein A-I (apoA-I) is the principal protein constituent of high-density lipoprotein (HDL). HDL has a strong anti-oxidant, anti-inflammatory, and anti-atherosclerotic activity in blood. In this study, we investigated biological function of trans fatty acid in reconstituted HDL (rHDL) state.

Methods Fatty acids were incorporated in rHDL containing apoA-I and phospholipid (PL) (PL:fatty acid:apoA-I molar ratio 95:10:1).

Results The rHDL containing the elaidic acid (C18:1, trans) had much smaller particle size than native rHDL. Elaidic acid-rHDL treatment induced more cellular uptake of oxidized LDL (oxLDL) into macrophages and loss of anti-oxidant activity. Injection of elaidic acid-rHDL aggravated inflammatory deaths and zebrafish embryo development.

Conclusion Conclusively, rHDL containing elaidic acid showed pro-atherogenic and embryo toxic effect. Injection of the elaidic acid-rHDL resulted acute death of zebrafish embryo with more production of reactive oxygen species and attenuated developmental speed.

ICAO2013-145

MODIFICATION OF LIPOPROTEINS AND ATHEROSCLEROTIC EFFECT BY ENVIRONMENTAL PHTHALATES IN HUMAN CELLS AND ZEBRAFISH

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Objective Phthalates are contaminated in widely used products of plastics and medical devices. Phthalates has been concerned because of their potential risk for human exposure and animal toxicity studies. In this study, dose–dependent toxic effect of phthalate were investigated in human lipoprotein and zebrafish.

Methods Treatment (final 50 mM) of phthalate into a human apoA-I, lipoproteins and human cells, macrophage, dermal fibroblast. The zebrafish were exposed water containing of 11 and 22 ppm phthalate under consumption normal (ND) or high cholesterol diet (HCD). Zebrafish embryos were exposed to water containing phthalate (at the 11 and 22 ppm, respectively).

Results In this study, lipid-free apoA-I showed no remarkable difference on phthalate treatment, but human plasma HDL_3 showed multimerization (phthalate final 50 mM) of apoA-I. The phthalate promoted more foam cell formation via acceleration phagocytosis of LDL into macrophages and caused aging in human dermal fibroblast at the same concentration. Zebrafish in water containing of phthalate, ND groups displayed 59% and 49% decreases of plasma TC (total cholesterol) and TG (triglyceride) levels. HCD groups showed the same decrease pattern around 45% and 32% decreased than control, respectively. Zebrafish embryos, which were exposed to water containing phthalate, showed early death (only 6% embryo survivability at high concentration) with increase of reactive oxygen species (ROS) and attenuated developmental speed.

Conclusion Phthalate have a strong pro-atherogenic properties via severe modification of lipoproteins, human dermal cells and macrophages. Exposure of embryo in phthalate could induce the pro-inflammatory effect with slow development.

Menopause

ICAO2013-067
OXIDATIVE STRESS IS ASSOCIATED WITH C-REACTIVE PROTEIN IN NON-DIABETIC POSTMENOPAUSAL WOMEN, INDEPENDENT OF OBESITY AND INSULIN RESISTANCE

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Objective Oxidative stress is associated with obesity, metabolic syndrome, and inflammation, suggesting it could be an early event in the pathology of chronic diseases. We tested the hypothesis that elevated levels of oxidative stress markers are associated with increased C-reactive protein (CRP) and that this is independent of obesity and insulin resistance.

Methods This study was cross-sectional designed and non-diabetic postmenopausal women (n=1821) with CRP levels ≤10 mg/L was enrolled. The CRP levels were categorized into quartiles from the lowest to the highest concentrations (Q1-Q4). The degree of insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA-IR). We measured oxidative stress using urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) and plasma oxidized low-density lipoprotein (ox-LDL).

Results After adjustments for age and lifestyle habits, including smoking and drinking, we found higher body mass index (BMI) and HOMA-IR scores in Q2 and Q3 versus Q1. The Q4 BMI and HOMA-IR scores were higher than all other quartiles. The plasma ox-LDL was higher in Q4 than in Q1. Urinary 8-epi-$PGF_{2\alpha}$ was higher in Q3 and Q4 than in Q1 or Q2. Urinary 8-epi-$PGF_{2\alpha}$ positively correlated with CRP ($r=0.235$, $P<0.001$) whereas no correlation was found between ox-LDL and CRP. Multiple linear regression analyses of BMI and HOMA-IR showed that the association between urinary 8-epi-$PGF_{2\alpha}$ and CRP levels remained significant ($P<0.001$).

Conclusion Oxidative stress measured by increased concentration of urine 8-epi-$PGF_{2\alpha}$ is strongly associated with CRP levels. This finding was independent of obesity and insulin resistance in non-diabetic postmenopausal women.

Multiple linear regression analyses of the relationships between CRP, oxidative stress markers,and metabolic syndrome factors

	P1		*P2*	
	β coefficient (95% CI)[a]	*P* value	β coefficient (95% CI) [a]	*P* value
8-epi-$PGF_{2\alpha}$	0.487 (0.329, 0.646)	<0.001	0.504 (0.351, 0.658)	<0.001
Oxidized LDL	0.161 (-0.016, 0.338)	0.074	0.135 (-0.037, 0.307)	0.124
Triglycerides	0.389 (0.259, 0.519)	<0.001	0.224 (0.090, 0.358)	0.001
HDL-cholesterol	-0.592 (-0.827, -0.356)	<0.001	-0.372 (-0.607, -0.137)	0.002
Systolic BP	0.005 (0.001, 0.009)	0.025	0.000 (-0.004, 0.004)	0.968
Diastolic BP	0.005 (-0.002, 0.011)	0.151	-0.002 (-0.009, 0.004)	0.479

[a]Confidence interval. *P1*: Adjusted for age and lifestyle. *P2*: Adjusted for age, lifestyle, BMI, and HOMA-IR. Calculation of triglycerides, HDL-cholesterol, HOMA-IR, oxidized LDL, and 8-epi-$PGF_{2\alpha}$ were based on log-transformed values.

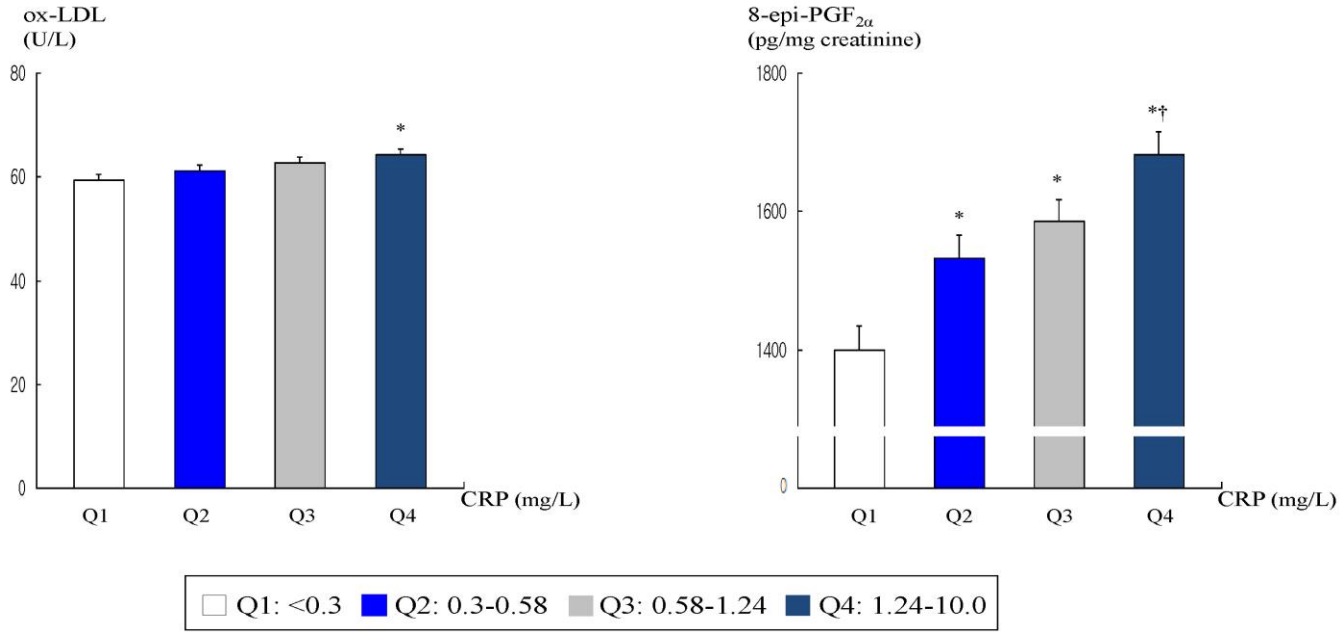

Figure 1. Comparison of plasma ox-LDL and urinary 8-epi-$PGF_{2\alpha}$ in 1821 non-diabetic postmenopausal women between the CRP quartiles (Q1-Q4) after adjusting for age and lifestyle.
Mean ± SE., P-values derived from ANOVA with Bonferroni correction. *p<0.05 compared with the value in the Q1 tested by ANOVA (Bonferroni correction). †p<0.05 compared with the value in the Q2 tested by ANOVA (Bonferroni correction).

Metabolic Syndrome

ICAO2013-078

METABOLIC SYNDROME AS A PREDICTOR OF CARDIOVASCULAR DISEASES: A KOREAN COMMUNITY-BASED PROSPECTIVE COHORT STUDY

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Objective The purpose of this longitudinal study was to investigate whether the presence of the NCEP-ATP III defined metabolic syndrome (MetS) is associated with the risk for future development of cardiovascular diseases (CVD; coronary heart disease and stroke) in Koreans.

Methods The study subjects were from the Korean Health and Genome Study (KHGS). 9,128 subjects (4,375 men and 4,753 women), 40 to 69 years of age, were enrolled and evaluated for the development of new onset CVD from 2001 to 2012 (median 8.2 years of follow-up).

Results The prevalence of the MetS at baseline was 22.0% (932/4241) and 29.7 % (1383/4657) in men and women respectively, and the MetS was found to be associated with the risk for CVD (OR 1.670, 95% CI 1.399 – 1.992, $p < 0.001$). More specifically, MetS was associated with the risk for future CVD in both men and women (OR 1.689, 95% CI 1.295 – 2.204 in men, OR 1.686, 95% CI 1.007 – 2.192 in women). In addition, age (OR 1.077, 95% CI: 1.067 – 1.087, $p < 0.001$), current smoker (OR 1.332, 95% CI: 1.105 – 1.607, $p = 0.003$), HOMA-IR (OR 1.066, 95% CI: 1.020-1.115, $p = 0.005$) and LDL (OR 1.002, 95% CI: 1.000-1.005, $p = 0.037$) were independent predictive factors of CVD in this study.

Conclusion The NCEP-defined MetS was found to be associated with the risk for future CVD. Moreover, higher number of the MetS components was correlated with higher risk of CVD.

ICAO2013-103

A NOVEL HSD11B1 INHIBITOR PROVIDES GLYCEMIC AND LIPID CONTROL ALONG WITH SIGNIFICANT REDUCTION IN WEIGHT IN C57BL6/J MICE ON HFD

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Objective Increased 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) activity has been associated with metabolic syndrome including hyperglycemia. In this regard, selective inhibitors of HSD11β1have considerable potential for treating type 2 diabetes mellitus and other co-morbidities associated with the metabolic syndrome. In the present study, we investigated *in vitro* and in diet-induced obese (DIO) mice the anti-hyperglycemic effects of CNX-10-49: a novel and selective HSD11β1inhibitor

Methods ChoK1 cells stably expressing human HSD11β1gene and differentiated C2C12 were used for determination of IC50 for both human and mouse isoform. 3T3-L1 preadipocytes were used to evaluate adipocytes differentiation and lipolysis. Fully differentiated C2C12 cells and primary mouse hepatocytes were used to study the impact on glucose metabolism and hepatic glucose output respectively. Male C57BL/6 mice fed with chow diet (10% fat diet) or high fat diet (HFD) (60% fat diet) for 11 weeks. HFD fed animals were assigned to either vehicle or CNX-01-49 (30 mg/kg, po BID) treatment groups (n=8) for 9 weeks.

Results CNX-10-49 has an IC50 of 5nM and 66nM towards human and mouse HSD11β1 isoforms respectively. CNX-10-49 suppressed cortisone-induced triglyceride accumulation in 3T3-L1 cells. CNX-10-49 also significantly inhibited cortisone and Isoproterenol mediated lipolysis by ~30% in 3T3L1 adipocytes. In C2C12 cells, CNX-10-49 reduced mRNA expression of PDK4 and TRIM63. In primary mouse hepatocytes CNX-10-49 inhibited gluconeogenesis significantly by 15%. Treatment of C57BL/6 DIO mice on HFD with CNX-10-49 significantly reduced fasting glucose by ~12% (196±4.31 in HFD Vs 173±5.35 mg/dl in treatment), fasting insulin by 3 folds and fasting plasma glycerol level by 15%. Compared to HFD mice control animals plasma triglycerides were significantly reduced in mice trated with CNX-10-49 (217±9.34 in HFD Vs 175±9.06 mg/dl CNX-10-49 treated). Even though there was no change in the feed intake body weight was reduced significantly by ~15% (39.3±0.64 in HFD Vs 32.83±1.24 g in treatment). Glucose excursion, during OGTT, was significantly reduced by ~13%; (glucose AUC 57376±1382 in HFD Vs 49680±734 in treatment)

Conclusion Taken together, our data suggests that CNX-10-49, a selective HSD11β1 inhibitor, may provide significant glycemic and lipid control in type 2 diabetic patients with additional impact on body weight

ICAO2013-135

SERUM HSCRP LEVELS IN CENTRALLY OBESE SUBJECTS WITH OR WITHOUT METABOLIC SYNDROME (MS)

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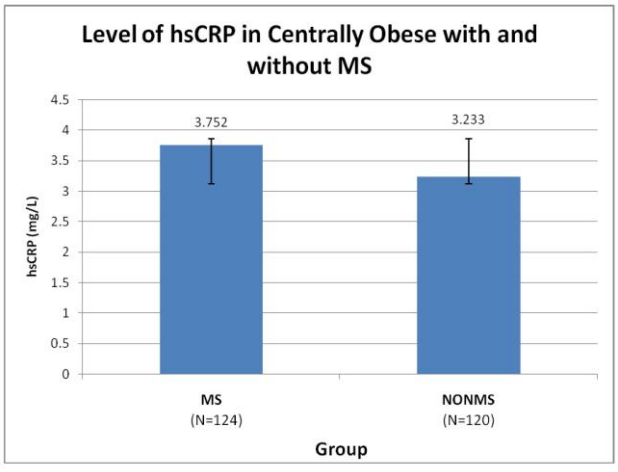
Objective Central obesity is the key component of metabolic syndrome (MS). High sensitivity C-Reacrtive Protein (hsCRP) is an inflammatory marker produced by adipocytes which are found to be predictive for coronary artery disease (CAD). This study aims to evaluate the levels of serum hsCRP in centrally obese subjects with or without metabolic syndrome and to compare the concentrations of hsCRP in centrally obese subjects with number of MS components presence.

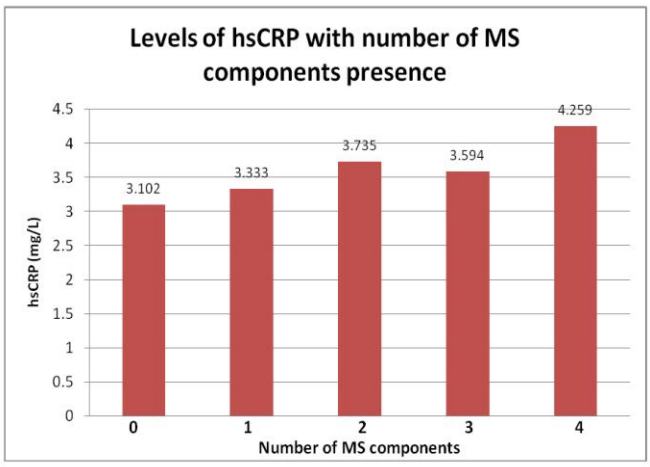
Methods 244 subjects (83 males and 161 females, age (mean±SD) : 47.52±8.4) were recruited from UiTM specialist clinics and community health screenings and divided into 2 groups; MS and NonMS group. Based on the International Diabetes Federation (IDF) 2005, MS was defined as centrally obese (waist circumference ≥ 90cm and ≥ 80cm for male and female respectively) with at least presence of two MS components (fasting plasma glucose ≥5.6mmol/L, blood pressure ≥130/85mm Hg, triglycerides level ≥1.7mmol/L and HDL-cholesterol <1.0mmol/L for males or <1.3mmol/L for females). Obese subjects not fulfilling this fell into the NonMS group.Fasting blood samples were collected and serum lipid profile and hsCRP were measured using enzymatic reference method on an automated analyzer (Cobas Integra 400, Roche Systems, Germany).

Results There was no significant differences in the levels of hsCRP between MS and NonMS subjects (mean±SD : 3.75mg/L ± 2.77 vs 3.23mg/L ± 2.51, $p>0.05$). Concentrations of hsCRP (mean±SD : 3.10mg/L ± 2.5, 3.33mg/L ± 2.54, 3.74mg/L ± 2.94, 3.59mg/L ± 2.68 and 4.26mg/L ± 2.51 respectively, $p>0.05$) were not significant with number of MS components; 0, 1, 2, 3 and 4 respectively .

Conclusion These findings suggest that there are no significant differences in hsCRP levels between obese subjects with or without MS and having either 0 to 4 other MS components.



Data are expressed as Mean ± SD, $p > 0.05$ when compared with NonMS group



Data are expressed as Mean ± SD, $p > 0.05$

ICAO2013-175

METABOLIC SYNDROME AND ALANINE AMINOTRANSFERASE LEVELS IN HEALTHY KOREAN ADOLESCENTS

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Objective The potential interactions between components of metabolic syndrome (MetS) and alanine aminotransferase (ALT) have not been fully investigated in healthy adolescents. The study investigated the impact of a mild ALT elevation on the prevalence and risks of MetS in healthy Korean adolescents.

Methods From the Korean National Health and Nutrition Examination Surveys 1998-2009, the data of 5,026 adolescents aged 10-18 yr (2,604 boys and 2,422 girls) were analyzed. Individuals who had ALT levels equal or more than 40 IU/L were excluded.

Results The mean ALT level was higher in boys (15.4 IU/L) than in girls (12.7 IU/L, $P < 0.0001$). Subjects in the upper ALT tertile had higher mean values of BMI, waist circumference, blood pressure, triglyceride and homeostasis model assessment-insulin resistance, and increased prevalence of MetS than subjects in the lower tertile ($P <0.0001$). The risk of each five components of MetS was significantly higher than subjects in the lower tertile ($P <0.0001$). The prevalence of MetS increased with the elevation of obesity level, and it increased further with elevation of ALT tertile. Compared with the subjects in the lower ALT tertile, the prevalence of MetS was higher in the upper tertile among obese adolescents (44.6-50.7 vs. 31.2-40.0%) as well as normal-weight adolescents (5.2-7.7 vs. 2.7-3.2%). Subjects in the upper ALT tertile were at a higher risk of MetS than those in the lower tertile (OR=1.95 for boys, OR=2.00 for girls) after controlling for age and BMI.

Conclusion A high serum ALT within normal range increased the risk of all the components of MetS. According to the elevation of ALT tertile, the prevalence of MetS increased in obese adolescents and normal weight adolescents as well. Thus, serum ALT levels in addition to BMI might be useful as a marker for early detection of MetS.

Nutrition

ICAO2013-30

RELATIONSHIP BETWEEN SERUM PHOSPHOLIPID FATTY ACIDS AND FASTING GLUCOSE STATUS: ASSOCIATED WITH EARLY RISK OF TYPE2 DIABETES AND CARDIOVASCULAR DISEASE

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Objective Alteration in blood or dietary fatty acid (FA) composition may be associated with insulin resistance (IR) and the related disorder. However, there were few studies for the association of serum phospholipid FA composition with fasting glucose in non-metabolic syndrome (MetS), and its association with early risk of type2 diabetes and cardiovascular disease.

Methods In a cross-sectional study among healthy subjects (n=2022, 30~69yrs), serum phospholipid FAs, desaturase activities, fasting glucose, insulin, free fatty acid, and other cardiometabolic risk parameters (i.e. lipid profiles, inflammation, oxidative stress and lipid peroxidation) were compared between normal fasting glucose (NFG) and impaired fasting glucose (IFG) subjects.

Results Among serum phospholipid FA proportions, total monounsaturated FA (MUFA), oleic acid (OA, C18:1w9), dihomo-g-linolenic acid (DGLA, C20:3w6), delta-9-desaturase (D9D, C18:1w9/C18:0) and C20:3w6/C18:2w6 were significantly higher in IFG subjects than NFG controls. When subjects were subdivided into MetS and nonMetS, proportion of palmitoleic acid (PA, C16:1) was highest in IGF-MetS subjects and lowest in NFG-nonMetS ones. OA and D9D were highest in IGF-MetS group than the other 3 subgroups. DGLA and C20:3w-6/C18:2w-6 were higher in MetS subjects than nonMetS ones regardless of fasting glucose levels. hs-CRPs were higher in IFG subjects than NFG ones regardless of MetS status. Interestingly, hs-CRP levels in NFG subjects were significantly higher in MetS ones than nonMetS ones, but which was not observed in IFG subjects. Ox-LDL levels were higher in IFG-MetS group than the other 3 subgroups. 8-epi-PFG_{2a} levels were significantly higher in IFG subjects than in NFG ones regardless of MetS status. Among FA compositions, total MUFA, OA and D9D showed relatively high-positive correlation with fasting glucose, HOMA-IR, TG, hs-CRP and 8-epi-PFG_{2a}. PA also positively correlated with TG and hs-CRP. Additionally, DGLA (C20:3w6) positively correlated with HOMA-IR, TG, hs-CRP and oxidized LDL. C20:3w6/C18:2w6 also positively correlated with TG, hs-CRP and oxidized LDL.

Conclusion Serum phospholipid total MUFA and OA, and D9D were mainly related to glucose metabolism and the related parameters. It suggests that changes in serum phospholipid FA composition, particularly MUFAs may be associated with the early alteration of glucose metabolism, and contribute to the risk of type2 diabetes and cardiovascular disease.

ICAO2013-31

INVERSE ASSOCIATION OF SERUM PHOSPHOLIPID DOCOSAHEXAENOIC ACID AND ARTERIAL STIFFNESS

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Objective Blood or dietary fatty acids (FAs) are known to be associated with cardiovascular disease. However, the results are still controversial. We aimed to examine the differences of serum phospholipid FAs compositions between healthy people and coronary artery disease (CAD) patients, and to investigate the association of FA compositions with cardiovascular risk and arterial stiffness expressed by brachial-ankle pulse wave velocity (ba-PWV).

Methods In a case-control study [healthy men (n=499) and CAD male patients (n=111), 30-69 years], serum phospholipid FA compositions and cardiovascular risk related parameters were measured. In healthy controls, ba-PWV was additionally measured to investigate the association with FA composition.

Results Basic parameters including lipid profiles, fasting glucose, insulin and HOMA-insulin resistance (IR) were significantly different between healthy men and CAD patients. Serum phospholipid FA compositions were also significantly different between the two groups, which maintained after adjusted for age, body mass index, cigarette smoking habit, alcohol consumption and dietary intake: linoleic acid (LA, C18:2w-6), eicosadienoic acid (EDA, C20:2w-6), docosahexaenoic acid (DHA, C22:6w-3) were lower, and palmitic acid (PA, C16:0), monounsaturated FA (MUFA), oleic acid (OA, C18:1w-9), dihomo-g-linolenic acid (DGLA, C20:3w-6), arachidonic acid (AA, C20:4w-6) and w6-polyunsaturated FA(w6-PUFA)/w3-PUFA were higher in CAD patients than in health controls. In correlation analysis, DHA was highly correlated with most of long-chain FAs. Healthy controls were subdivided into three groups according to DHA composition: lower (<2.061%), middle (2.061%~3.235%) and higher tertile (>3.235%). Fasting glucose, insulin and HOMA-IR were significantly higher in lower tertile group than in higher tertile group. ba-PWVs were also significantly higher in lower tertile group than in higher tertile group, which maintained after adjusted for age, cigarette smoking, alcohol consumption, and fat intake %.

Conclusion Serum phospholipid FA compositions were significantly different between CAD patients and health people. Additionally, this study suggests that lower proportion of serum phospholipid DHA may be associated with the increased cardiovascular risk including arterial stiffness.

ICAO2013-142

DIETARY AUTOPSY FOR ASSESSMET OF FOOD CONSUMPTION PATTERN AMONG DECEDENTS DYING DUE TO VARIOUS CAUSES OF DEATH

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Objective Dietary patterns characterized with increased refined carbohydrates, trans fat, saturated fat and w-6 fat are associated with greater risk of deaths due to cardiovascular diseases (CVDs). We examine the dietary patterns of victims via a dietary autopsy questionnaire, to find out its accuracy, in relation to causes of death.

Methods We studied the randomly selected records of death of 2222 (1385 men and 837 women) decedents, aged 25-64 years, out of 3034 death records overall from the records at Municipal Corporation. Causes of death were found out from family members, by scientist-administered, informed-consented, verbal autopsy questionnaire, completed with the help of the spouse and local treating doctor practicing in the appropriate health care region, based on available hospital records. Dietary intakes of the dead individuals were estimated by finding out the food intake of the spouse from 3- day dietary diaries and by asking probing questions about differences in food intake by the decedents using food measures and food models.

Results The score for prudent foods was significantly greater for deaths due to 'injury' miscellaneous causes compared to deaths due to non-communicable diseases (NCD). Multivariate logistic regression analysis revealed that after adjustment of age, total prudent foods (OR, CI 1.11; 1.06-1.18 men; 109;1.04-1.16 women) as well as fruits, vegetables, legumes and nuts (1.07; 1.02-1.12 men; 1.05; 1.99-1.11 women) were independently, inversely associated whereas Western type foods (OR, CI 1.02; 0.95-1.09 men; 1.00; 0.94-1.06 women); meat and eggs(1.00-0.94-1.06 men; .098; 0.93-1.04 women)and refined carbohydrates (0.98; 0.91-1.05 men, 0.95; 0.89-1.02 women) social class 3-5 and body mass index were positively associated with deaths due to NCDs.

Conclusion Causes of deaths and dietary intakes, can be accurately assessed by a modified verbal autopsy questionnaire based on medical records and interview of the family members. Increased intake of Western type foods and decline in prudent foods intake may be a risk factor for deaths due to NCDs.

Obesity

ICAO2013-028

FBXO9 IS REQUIRED FOR THE DIFFERENTIATION OF ADIPOCYTES

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Objective F-box protein 9 (FBXO9) is a member of SCF (Skp, Cullin, F-box)-type ubiquitin E3 ligases. In this study, we investigated a functional role of FBXO9 in the differentiation of adipocytes.

Methods Expression of FBXO9 was compared between obese mice and lean mice using qRT-PCR. FBXO9 was knocked down using siRNAs against FBXO9 in 3T3-L1 preadipocytes and then differentiation of adipocytes was monitored by Oil red-O staining. The expression levels of adipogenic regulators during adipocytes differentiation were determined using qRT-PCR and Western blot analysis.

Results FBXO9 was highly expressed in the obese mouse models such as high fat diet-fed mice and *db/db* mice, and expression of FBXO9 increased in the early stages of adipocyte differentiation of 3T3-L1. When siRNAs against FBXO9 were transfected one day before or simultaneously with the induction of differentiation, adipogenesis was significantly inhibited. In contrast, a treatment of FBXO9 siRNAs one day after the differentiation induction did not affect adipocytes differentiation. When FBXO9 was knocked down before the stimulation of differentiation, C/EBPb was not fully induced and expression of PPARg was almost completely inhibited. In addition, reduction of Wnt signaling molecules, such as LRP6 and b-catenin, upon the induction of differentiation was attenuated by knockdown of FBXO9. Interestingly, the inhibitory effect of FBXO9 knockdown on adipogenesis was barely observed in C/EBPb-stably expressing cells.

Conclusion These results suggest that FBXO9 is required for the differentiation of adipocytes,and C/EBPb probably mediates the effect of FBXO9 in adipogenesis.

ICAO2013-038

ASSOCIATION BETWEEN MONOCYTE CHEMOATTRACTANT PROTEIN-1(MCP-1) 2518A/G POLYMORPHISM WITH OBESITY IN KOREAN TYPE 2 DIABETES

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Objective MCP-1 is a chemokine to produce superoxides anions and to increase adhesion molecule expression on monocyte. The aim of this study was to evaluate the association of MCP-1 2518A/G polymorphism with obesity in Korean type 2 diabetes.

Methods We conducted a case-control study, which enrolled 526 subjects with Korean type 2 diabetes, and genotyping of MCP-1 2518A/G polymorphism was performed using polymerase chain reaction followed by digestion with *Puv II* restriction enzyme.

Results The prevalence of MCP-1 2518A/G polymorphism in diabetic patients was 13.2%(AA), 47.1%(AG) and 39.7%(GG) respectively. The prevalence of obesity was significantly higher (P<0.05) in diabetic patients with the MCP-1 2518 AA type (58.1%, n=43) compared to those with either the AG/ or GG type(43.8%, n=198). The prevalence of other micro and macro-complications were not different according to the MCP-1 2518A/G except proliferative diabetic retinopathy.

Conclusion These results suggest that the MCP-1 2518A/G polymorphism could be used as a risk factor for the development of obesity in Korean type 2 diabetes.

ICAO2013-042

REDUCTION OF SURVIVABILITY WITH OBESITY AND DIABETIC INDUCTION BY CO-CONSUMPTION OF FRUCTOSE AND CHOLESTEROL

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Objective In order to investigate physiological effect of fructose under hypercholesterolemia, zebrafish consumed fructose and cholesterol diet.

Methods Zebrafish consumed fructose (66% in wt/wt) with normal diet (ND) or high cholesterol diet (HCD, 4% cholesterol in wt/wt) for 7 weeks.

Results Fructose could modify the high-density lipoprotein (HDL) in functional and structural correlations. Treatment of fructose caused premature cellular senescence in human dermal fibroblast cell. Microinjection of fructose into zebrafish embryo caused more inflammatory response under co-presence of oxidized LDL (oxLDL). Zebrafish consumed fructose (66% in wt/wt) with normal diet (ND) or high cholesterol diet (HCD, cholesterol 4% in wt/wt) for 7 weeks. Survivability was 35% decreased in HCD + fructose group compared with ND + fructose group, while body weight gain was highest in HCD + fructose group. Interestingly in HCD + fructose group, serum cholesterol level was increased, however, serum TG was 35% more lowered than ND + fructose group. Fatty liver change was occurred in the both fructose containing group. Tail fin regeneration ability was degenerated in fructose-treated group.

Conclusion In conclusion, co-consumption of fructose and cholesterol induced lower survivability and obesity with hepatic inflammation via modification of lipoprotein: indicating acceleration of diabetic change. (Park GY and Hwang MJ are co-first authors.)

ICAO2013-044

DEFICIENCY OF CLUSTERIN EXACERBATES HIGH FAT DIET-INDUCED RENAL DISEASES

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Objective We examined the role of clusterin in high fat-induced renal disease in high fat-fed clusterin knockout (KO) and wild-type mice.

Methods Seven-week-old male C57BL/6 wild-type and clusterin knockout mice were fed a normal chow or high-fat diet for 8 weeks. Kidney tissues were stained with periodic acid Schiff (PAS) for renal histopathology and trichrome for fibrosis. Gene expressions of type Ⅰ collagen, matrix metalloproteinase (MMP)-2, fibronectine and lipid regulatory factors in the kidney were examined by quantitative RT-PCR.

Results Body weight and fat mass were increased in both wild-type and clusterin KO mice after high fat diet. Kidney weight to body weight ratio was significantly decreased in high fat-fed clusterin KO mice compared with high fat-fed wild-type mice. Plasma levels of triglyceride were increased by high fat diet in both wild-type and clusterin KO mice and there was no difference between two groups. Triglyceride levels in kidney were increased by high fat-fed clusterin KO mice compared with chow-fed wild-type mice. Levels of HDL and total cholesterol were not different among the groups. PAS staining in mesangial area and trichrome staining in tubulointerstitial area were increased in clusterin KO mice compared with wild-type mice in chow diet group. PAS and trichrome staining were increased in wild-type mice by high fat diet and they were further increased in high fat-fed clusterin KO mice. Gene expression of collagen 1, fibronectin, and MMP2 were increased in chow-fed clusterin, high fat-fed wild-type, and high fat-fed clusterin KO mice compared with chow-fed wild-type mice and there was no significant difference among these three groups. Gene expression of collagen 4 was increased in high fat-fed clusterin KO mice compared with chow-fed wild-type mice. Gene expression involved in lipid uptake was increased by deficiency of clusterin and high fat diet had no affect on the gene expression. Gene expression involved in lipid efflux was increased by deficiency of clusterin or high fat diet. Gene expression involved in lipid catabolism was reduced in high fat-fed clusterin KO mice.

Conclusion These results suggest that deficiency of clusterin exacerbates high fat diet-induced renal diseases through increased lipid accumulation.

ICAO2013-049

DANSHEN EXTRACT INCREASES UCP-1 EXPRESSION AND PREVENTS MITOCHONDRIAL DYSFUNCTION AND OBESITY BY ACTIVATING AMPK AND PGC-1A IN BROWN ADIPOSE TISSUE

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Objective Obesity is a medical condition resulting from an imbalance between energy intake and expenditure. Brown adipose tissue (BAT) is important for energy expenditure and stimulated BAT can convert large amount of calories to heat generation alone due to mitochondrial uncoupling. Many studies suggested that obesity is accompanied by diminished or disrupting BAT function. PGC-1α(peroxisome proliferator-activated receptor γ coactivator) controls mitochondrial biogenesis in BAT and brown fat differentiation to adaptive thermogenesis. PGC-1α interacts with PPAR γ in brown adipocytes to enhance the expression of brown fat specific uncoupling protein 1 (UCP1). Therefore, promoting BAT function has therapeutic potential to combat obesity.

Methods Danshen, dried root of Salvia miltiorrhiza, is one kind of traditional Chinese medicine that has many effects on metabolic diseases. However, the mechanisms by which Danshen extract (DE) functions as a metabolic regulator remain largely unknown.

Results Here we demonstrate that DE regulates energy homeostasis in brown adipocytes through activation of AMP-activated protein kinase (AMPK), resulting activation of its downstream target, PGC-1α. The activation of these key metabolic sensors results in enhancement of uncoupling protein 1(UCP-1), known as thermogenin, accounting for the beneficial metabolic effects of DE.

Conclusion These results indicate that DE regulates energy expenditure through an AMPK-PGC-1 α-dependent mechanism in adipocytes.

ICAO2013-082

THE ASSOCIATIONS OF SLEEP DURATION WITH BMI, EATING HABITS AND SEDENTARY BEHAVIORS AMONG KUWAITI ADOLESCENTS

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Objective To determine whether BMI, eating habits and sedentary behaviors are associated with sleep duration among Kuwaiti adolescents

Methods The study is part of the Arab Teens Lifestyle Study (ATLS), which is a school-based cross-sectional multi-center collaborative study. A sample of 906 adolescents (boys and girls) aged 14-19 years was randomly selected from 6 Kuwaiti Governances using a multistage stratified cluster sampling technique. Anthropometric data, eating habits, sedentary behaviors and sleep duration of the participants were measured using ATLAS self-reported questionnaire. The associations of sleep duration with body mass index (BMI), waist circumference (WC), eating habits and sedentary behaviours were examined using the General Linear Model expressed in P value and partial Eta Squared (proportion of variance).

Results The prevalence of overweight and obesity was 50.5% in boys and 46.5% in girls. The majority of boys (76%) and of girls (74%) fell into the short sleep duration category (6 hours/day or less). Sleep duration were found to be negatively associated with BMI (girls only). According to sedentary behaviors, watching television (boys and girls) and working on computers (boys only) were also negatively associated with sleep duration. While the consumption of breakfast (both genders) and milk (boys only) were positively associated with sleep duration ($p < .05$). In contrast, the consumption of fast foods (both genders), sugary drinks and sweets (boys only) potatoes (girls only) were negatively associated with sleep duration ($p < .05$). In general, the proportions of variance (expressed in partial eta square) in the anthropometric data, eating habits, sedentary behaviors explained by sleep duration were found to be less than 2.9% in boys and less than 2.6% in girls.

Conclusion Short sleep duration was associated with obesity measure, a combination of poor eating habits and more sedentary behaviors. The findings also suggest gender differences in these associations. Therefore, adequate sleep is an important modifiable risk factor to prevent obesity and was positively associated with some lifestyle habits.

Table 1.The associations of sleep duration with BMI, WC, sedentary behaviours, and eating habits.

	Boys		Girls	
Independent Variables	P value[1]	PES [2]	P value[1]	PES [2]
Body mass index	0.193	0.004	0.029	0.011
Waist circumference	0.392	0.002	0.663	0.000
TV hours	0.000	0.029	0.001	0.026
Computer hours	0.002	0.020	0.362	0.002
Breakfast	0.024	0.011	0.051	0.009
Sugar drinks	0.001	0.024	0.365	0.002
Vegetables	0.131	0.005	0.800	0.000
Fruits	0.453	0.001	0.180	0.004
Milk	0.039	0.009	0.876	0.000
Fast foods	0.034	0.010	0.007	0.017
Potatoes	0.370	0.002	0.009	0.016
Sweets	0.022	0.011	0.346	0.002
Energy drinks	0.055	0.008	0.793	0.000

[1] P value: The mean difference is significant at the 0.05 level or less.
[2] PES: partial eta squared (proportions of variance).

ICAO2013-117
SUPPLEMENTATION OF KETOHEXOSES INDUCE OVERWEIGHT WITH INFLAMMATION IN ZEBRAFISH

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Objective The purpose of this study is to Induce overweight using zebrafish by ketohexose supplementation.

Methods In order to induce obesity by ketohexose supplementation in diet, we compared physiological effect of the fructose, tagatose, psicose in zebrafish for 8 weeks.

Results Fructose-fed group showed the highest bodyweight (54% increase from initial bodyweight). However, tagatose and psicose group showed lower level of bodyweight 15% and 22% respectively compared with control. Interestingly, the psicose-fed group showed serum triglyceride level was the highest (17% higher than fed a control, normal diet). While fructose-fed group showed the highest level of serum glucose level. Tagatose-fed group showed the smallest fatty liver damage and inflammation.

Conclusion In conclusion, fructose among ketohexose supplementation could induce more severe obesity and hepatic inflammation. (JMB and JAY are co-first authors).

ICAO2013-119

ANTI-OBESITY AND HYPOLIPIDEMIC EFFECT OF ß-LAPACHONE IN HYPERCHOLESTEROMIC ZEBRAFISH

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Objective ß-lapachone is involving apoptosis and aging process. Although it has been well known that ß-lapachone can enhance body function in aged animal. However, there has been not enough reprort its anti-obesity effect in vertebrates.

Methods Four weeks consumption of ß-lapachone (final 0.1% and 0.2% in tetrabit wt/wt) resulted the least gaining of body weight, up to 9% reduction of body weight compared with high cholesterol diet (HCD) control.

Results Serum cholesterol and triaglyceride (TG) were decreased upto 23% and 46%, respectively, compared with high cholesterol diet (HCD) control. Although the serum glucose level was decreased (upto 33%), the serum cholesteryl ester transfer protein (CETP) activity was not changed. Serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) level was improved by the consumption. Fatty liver change, which was caused by HCD consumption, was remarkably ameliorated in the ß-lapachone group. Histologic analysis revealed that oil-red O stained area and reactive oxygen species (ROS)-stained area are concomitantly diminished by the ß-lapachone consumption.

Conclusion Conclusively, ß-lapacone consumption caused antiobesity effect via enhancement of serum lipid and hepatic fatty acid clearance.

ICAO2013-143

ASSOCIATION OF INCREASED MORTALITY WITH OVERWEIGHT AND OBESITY AMONG URBAN DECEDENTS, DYING DUE TO VARIOUS CAUSES

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Objective While overweight and obesity are important risk factors of death due to cardiovascular disease (CVD) and diabetes, underweight predisposes deaths due to infections. In the present study, we examine the association of BMI with causes of deaths among urban decendents in a middle income country.

Methods For the period 1999-2001, we studied the randomly selected records of death of 2222 (1385 men and 837 women) decedents, aged 25-64 years, out of 3034 death records overall from the records at Municipal Corporation, Moradabad. All the families of these decendents could be contacted individually to find out the causes of death, by doctor administered, informed consented, verbal autopsy questionnaire, completed with the help of the spouse and local treating doctor practicing in the appropriate health care region. Clinical data and causes of death were assessed by a questionnaire based on available hospital record and verbal autopsy questionnaire. The association of BMI with causes of death was calculated by Mantel-Haesnzel test.

Results Majority of the decedents (n=792, 35.6%) had normal BMI. The prevalence of underweight victims was 14.2%, overweight 29.4% and obese 20.8%. There was an overall increase in risk factors; diabetes mellitus, hypertension, and CAD among overweight and obese victims based on BMI criteria, and the trend was significant. BMI was positively associated with significant rising trend in the prevalence of circulatory causes of death, both among men and women. Infections and cancers as the cause of death were inversely associated with increase in BMI among both men and women. Injury and miscellaneous causes of death showed no association with BMI among men whereas among women, miscellaneous causes of death were positively and significantly associated with BMI. No such association was noted for injury with BMI among women. Among circulatory causes of death, 25.0% of the victims had normal BMI, which was because of victims dying due to rheumatic heart diseases and heart failure.

Conclusion Overweight and obesity are important determinant of mortality due to circulatory diseases and underweight due to infections. Those decedents dying of heart failure, rheumatic heart disease and cancers, may have underweight during the deaths, similar to those dying of infections.

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ICAO2013-152

CONTRIBUTION OF IGFBP-2 TO THE RELATIONSHIP OF VISCERAL ADIPOSITY TO GLUCOSE TOLERANCE IN MEN

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Objective IGF binding protein-2 (IGFBP-2) is a circulating protein that modulates glucose homeostasis and adipose tissue accumulation. In humans, low IGFBP-2 has been associated with obesity and insulin resistance. Little is known about IGFBP-2 associations with cardiometabolic risks. In this study, we aimed to quantify the associations between cardiometabolic risk variables and plasma IGFBP-2 and to determine whether IGFBP-2 is an independent predictor of insulin sensitivity in overweight men.

Methods In this cross-sectional study, 379 men (ages 20-65 yrs.) covering a wide range of body mass index (BMI) values were recruited through the media. Plasma IGFBP-2 concentrations, glucose tolerance and plasma lipid profile were determined after an overnight fast.

Results IGFBP-2 levels correlated with BMI (r = -0.59; $p < 0.0001$), waist circumference (r = -0.56; $p < 0.0001$) and with areas of visceral (VAT) (r = -0.45; $p < 0.0001$) and subcutaneous adipose tissue (r = -0.51; $p < 0.0001$). Subjects with higher VAT showed significantly lower concentrations of IGFBP-2 when compared to patients with low VAT, independently of their BMI status. Multivariate analyses indicated an independent role for adiponectin and triglycerides in predicting IGFBP-2 concentrations. Low IGFBP-2 status as defined by quartiles was strongly associated with glucose intolerance despite hyperinsulinemia during OGTT. Plasma IGFBP-2 levels were a robust independent predictor of the area under the curve of insulin concentrations during OGTT.

Conclusion These results suggest that lower IGFBP-2 levels are associated with a detrimental metabolic profile mediated by VAT accumulation. The strong relationship between IGFBP-2 levels and insulin levels suggests an important role for IGFBP-2 in visceral obesity-related insulin resistance.

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ICAO2013-179

GENOME-WIDE ASSOCIATION STUDY FOR THE INTERACTION BETWEEN BMR AND BMI IN KOREAN OBESE FEMALES

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Objective Basal metabolic rate (BMR), and the closely related resting metabolic rate (RMR), is the amount of energy expended daily by humans and other animals at rest. BMR accounts for approximately 45% to 70% of total energy expenditure in most healthy adults and affect by age, gender, body surface area, body composition, genetic composition, pregnancy and hormonal status directly. The aim of present study was to identify the genetic factors associated with the interaction of BMR and body mass index (BMI) in obese women.

Methods A genome-wide association analysis of 678,839 single nucleotide polymorphisms (SNPs) in 77 Korean obese and normal weight females was performed. Using regression and stepwise analysis, we investigated what factors preferentially involved in the interaction of BMR and BMI. Quantitative trait association analyses (PLINK) for BMR and BMI in 77 obese individuals (BMR>1426.3kcal/day and BMI>23kg/m^2) and normal-weight controls (BMR<1426.3kcal/day and BMI<23kg/m^2) were performed.

Results 140 SNPs achieved formal genome-wide statistical significance in this study ($P<1x10^{-4}$). There was a significant association between NRG3 gene SNPs in the 10q23.1 chromosomal region and BMR (rs10786764, $P=8.0x10^{-7}$). FGGY gene SNP rs6676078 also reached genome-wide significance ($P=8.3x10^{-5}$). Weaker associations ($P<1x10^{-5}$) with BMR were found in TNR, B3GNT2, FZD7, OR2Y1, MGAT1, NPAS3, PKD1L2 and SETBP1 genes. Seven other genes-related to BMI (HSD52, TMA16, MARCH1, DGKI, NRG1, NRXN3 and STK4) yielded $P<10x10^{-4}$. The five genes associated with BMR and BMI were NRG3, OR8U8, BCL2L2-PABPN1, PABPN1, and SLC22A17 ($P<1x10^{-4}$) in common.

Conclusion Twenty-two genes/chromosome regions reached genome-wide association significance ($P<1x10^{-4}$, 44 SNPs) in our GWAS. Five common genes (NRG3, OR8U8, BCL2L2-PABPN1, PABPN1, and SLC22A17) yielded $P < 1 \times 10^{-5}$ in BMR and BMI. Our findings provide new insights into the genetic etiology of obesity related to BMR. These results will serve as a resource for replication and validation identified with BMR and BMI.

Pathophysiology/Basic Science/Animal Studies

ICAO2013-039

CD137 SIGNALING IN ATHEROGENESIS

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Objective CD137 (4-1BB), a member of the TNF receptor superfamily, has been reported to be expressed in human atherosclerotic plaques and promotes development of plaque inflammation. We previously demonstrated that CD137 exacerbates atherosclerosis via combined actions on immune and vascular cells. However, the mechanism and signaling pathway that govern the role of CD137 in plaque stability of advanced atheroma are less understood.

Methods Here, we established atherogenic *ApoE*$^{-/-}$ and *ApoE*$^{-/-}$*CD137*$^{-/-}$ mice and these mice were fed with normal chow diet for 66 weeks. We performed immunohistochemistry to analyze advanced plaque phenotype and investigated the functional mechanisms of CD137 on both macrophages and vascular smooth muscle cells (VSMCs).

Results In atherosclerotic plaque lesion, CD137 was expressed on macrophages and VSMCs, which were major cells involved in atherosclerotic plaque stability. CD137 activated macrophages, and produced MMP-9 via P38 mitogen-activated protein kinase (MAPK) and ERK1/2 signaling pathways. Also, CD137 induced apoptosis of VSMCs migrated into intima, which was due to decreased anti apoptotic regulators such as Bcl-2 in VSMCs followed by up-regulation of cleaved caspase-3 in VSMCs. Furthermore, activation of CD137 signaling using agonistic anti CD137 (3E1) mAb induced plaque instability in atherosclerotic plaque lesion of high fat diet fed *Ldlr*$^{-/-}$ mcie.

Conclusion Together we think that CD137 signaling has an important role in advanced vulnerable plaque formation and this study provides more effective strategies for various cardiovascular diseases as well as introducing a valuable experimental model.

ICAO2013-040

SJJ1 DEFICIENCY ACCELERATES ATHEROSCLEROTIC PLAQUE FORMATION IN APOLIPOPROTEIN E-DEFICIENT MICE

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Objective A novel membrane protein SJJ1 is expressed on the cell surface. We showed that SJJ1 is weakly expressed in endothelial and myeloid cells under normal conditions, but is increased by inflammatory responses. However, the biological relevance of SJJ1 in inflammatory diseases remains unknown. We suggests that SJJ1 would have function as a novel inflammatory factor in atherosclerosis.

Methods To demonstrate that SJJ1 is related to atherosclerosis, we analyzed SJJ1-positive cells in the atherogenic aorta. First, we observed the expression level of SJJ1 in oxidized LDL-induced endothelial cells and macrophages. Next, we established SJJ1 knockout mice and SJJ1/ApoE double knockout mice. These mice were fed with western diet for 13 weeks. Then, we examined formation of atherogenic lesions in the aortic artery and sinus with oil red o staining.

Results We showed that SJJ1 is expressed on the cell surface via experimentally overexpression of SJJ1. In addition, Number of SJJ1 expressing cells was significantly increased in oxidized LDL-induced peritoneal macrophages as compared to non-treated control. We confirmed that SJJ1 is an inflammatory factor expressed activated macrophages. We also found that SJJ1 deficiency accelerate atherosclerotic plaque formation in ApoE knockout mice. Moreover, we observed that the rate of SJJ1-positive macrophage increased in advancing atherosclerotic aorta.

Conclusion In this study, we found that the expression of SJJ1 is increased in the infiltrated macrophage within advanced atherosclerotic plaques. Moreover, formation of atherosclerotic lesions accelerate via SJJ1 deficiency. Based on these data, we propose that it is necessary to SJJ1-expressing myeloid cells in atherosclerotic plaque to protect the chronic inflammatory disease.

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ICAO2013-048

EFFECT OF GINSENG EXTRACT ON OBESITY AND INFLAMMATION IN HIGH FAT DIET-INDUCED OBESE RATS

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Objective Obesity has become a worldwide health epidemic. It is reported to be highly associated with chronic low-grade inflammatory state, which leads to the development of metabolic dysfunction such as hypertension, atherosclerosis and insulin resistance. In this study, we investigated whether ginseng extracts attenuated obesity and inflammation in high fat diet-induced obese animals.

Methods Male Sprague-Dawley rats were divided into three groups and fed a 45% high-fat diet (CON), a 45% high-fat diet supplemented with 1.5% hot water extract of ginseng (WEG) or high hydrostatic pressure extract of ginseng (PEG) for 14 weeks. After the experimental period, the final body weight and white adipose tissue mass were measured. Lipid profiles in liver, serum and feces were analyzed and gene expression of adipogenic genes and inflammatory genes in adipose tissue were measured.

Results The final body weight and epididymal adipose tissue weight were decreased in the PEG group compared to those of CON group (P<0.05). Total lipid and triglyceride (TG) levels in liver and serum were also decreased in the PEG group (P < 0.05) compared to those of CON group. In addition, fecal TG excretion in the PEG group was significantly increased compared to that of CON group. The effects of WEG on the body weight, adipose tissue mass and lipid profiles in liver, serum, and feces were similar to those of PEG group, though there were no significant changes, compared to those of CON group. The mRNA expression of adipogenic genes such as peroxisome proliferator-activated receptor-γ (PPAR-γ) and activating protein 2 (aP2) were down-regulated (P < 0.05) by PEG. Furthermore, mRNA levels of pro-inflammatory genes including tumor necrosis factor-α (TNF-α), interlukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) were also reduced by the PEG compared to those of CON group (P < 0.05). In the WEG group, aP2 and TNF-α mRNA expression were also down-regulated compared to those of CON group.

Conclusion It is postulated that ginseng extract might have anti-obesity and anti-inflammatory effects via mechanism including down-regulation of adipogenic and pro-inflammatory genes. And the effects of PEG on obesity and inflammation looked greater than those of WEG.

TABLE Physiological variables of rats fed a CON, WEG, or PEG for 14wk [1]

Variables	CON	WEG	PEG
Initial Body Weight, *g*	99.33 ± 2.56	99.60 ± 1.81	99.20 ± 2.77
Final body weight, *g*	539.69 ± 14.60^{a}	502.67 ± 12.21^{ab}	490.56 ± 10.85^{b}
Food intake, *g/d*	19.85 ± 0.44	19.59 ± 0.57	19.15 ± 0.46
Energy intake, *kcal/d*	94.81 ± 2.12	93.58 ± 2.71	91.45 ± 2.17
Adipose tissue weight *g/100 g body weight*	3.37 ± 0.1^{a}	3.28 ± 0.14^{ab}	2.81 ± 0.13^{b}
Serum TG, *mmol/L*	0.96 ± 0.12^{a}	0.8 ± 0.05^{ab}	0.68 ± 0.04^{b}
Liver TG, *μmol/g*	9.42 ± 0.45^{a}	8.89 ± 0.4^{ab}	7.38 ± 0.38^{b}
Fecal TG, *μmol/g*	5.85 ± 0.67^{b}	7.36 ± 0.58^{ab}	9.6 ± 1.32^{a}

[1] Values are mean ± SEM, n=10. Means in a row with superscripts without a common letter differ, P < 0.05. CON, control group; WEG, 1.5% hot water extract of ginseng fed group; PEG, 1.5% high hydrostatic pressure extract of ginseng fed group.

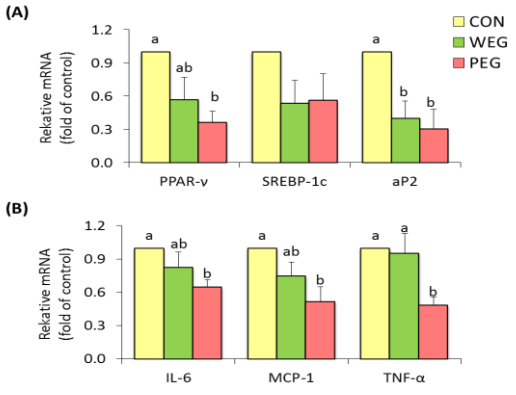

FIGURE Expression of genes involved in adipogenesis (A) and inflammation (B) in adipose tissue of rats fed a CON, WEG, or PEG for 14wk. Values are mean ± SEM, n=10. Means at a gene without a common letter differ, P < 0.05. CON, control group; WEG, 1.5% hot water extract of ginseng fed group; PEG, 1.5% high hydrostatic pressure extract of ginseng fed group.

ICAO2013-050

DEFICIENCY OF PEROXIREDOXIN I ENHANCES ATHEROGENIC PLAQUE PROGRESSION VIA CHOLESTEROL EFFLUX DYSFUNCTION

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Objective Atherosclerosis is characterized by an accumulation of lipids in the artery wall, together with infiltration of immunocytes. Especially infiltration of macrophages in intima was first step of atherosclerotic plaque formation. Peroxiredoxin Ⅰ (Prx Ⅰ), anti-oxidant enzyme, was first identified by a novel stress-inducible protein, MSP23 (macrophage 23-kDa stress protein). However, it has remained unclear what is the major cell type related Prx Ⅰ deficient induced atherosclerosis. This study aimed to elucidate the role of Prx Ⅰ in macrophage related atherosclerosis.

Methods First to investigate the effect of Prx Ⅰ deficiency in atherosclerosis, we established Apolipoprotein E (ApoE)-Prx Ⅰ double knock (DKO) mice. Next to identify the potential mechanisms underlying the pro-atherogenic effect of Prx deletion, we were examined the Prx Ⅰ expression in several cells and tissues. Finally, we confirmed that whether the anti-athrogenic effect of Prx Ⅰ is macrophage specific or not using bone marrow(BM) transplantation method.

Results The expression of Prx Ⅰ were remarkably higher in the peritoneal macrophages. And interestingly, when the fed western diet for 10 weeks, ApoE-Prx Ⅰ DKO BM transplanted ApoE KO mice showed increased plaque size more than ApoE KO BM transplanted mice. These result suggested that Prx Ⅰ may play pivotal role in macrophage lineage cells. Then we checked the macrophage in atherosclerotic plaque. As we expected, macrophage infiltration and foam cell formation were significantly increased under the Prx Ⅰ deficient mice. To understand the role of macrophage Prx Ⅰ in atherogenic signaling pathway, we check the macrophage cholesterol efflux pathways. Prx Ⅰ deficiency is associated with increase the plasma cholesterol and decrease the macrophage cholesterol efflux. We also observed that expression of scavenger receptor, CD36 was increased in Prx Ⅰ deficient macrophages. Interestingly, Prx Ⅰ deficient macrophages lead to reduced expression of ATP binding cassette transporter by uptake of oxidized lipoprotein

Conclusion These studies show that Prx Ⅰ in macrophages play more critical role in atherogenesis than the vessel wall's Prx Ⅰ. Moreover we found the novel mechanism which linked foam cell formation in Prx Ⅰ deficient macrophage.

ICAO2013-051

CP1 ATTENUATES ATHEROSCLEROSIS BY LOWERING SERUM CHOLESTEROL

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Objective Hyperlipidemia is a well-recognized risk factor of atherosclerosis, and can be induced by abnormal production of adipokines. CP1 (Cholesterol homeostasis-regulating protein-1) is an adipokine that is expressed highly by white adipose tissue (WAT) and is induced under the diet/energy intake. However, direct relationship between CP1 and circulating lipids is unclear. Here, we reveal the protective role of CP1 in the pathogenesis of hyperlipidemia and atherosclerosis for the first time.

Methods We identified the serum level of CP1 under hyperlipidemia by feeding high-fat diet (HFD) to wild type C57BL/6j mice for 1, 4, and 8 weeks. Next, we generated knockout mice lacking-*CP1* (*CP1*$^{-/-}$) or transgenic mice overexpressing-*CP1* (*CP1* tg) and cross-bred with hyperlipidemic *Ldlr*-deficient (*Ldlr*$^{-/-}$) mice to produce *Ldlr*$^{-/-}$*CP1*$^{-/-}$ or *Ldlr*$^{-/-}$*CP1* tg mice. To study the role of CP1 in hyperlipidemia and atherosclerosis *in vivo*, *Ldlr*$^{-/-}$*CP1*$^{-/-}$ or *Ldlr*$^{-/-}$*CP1* tg mice were mainly used.

Results Serum level of CP1 was markedly increased in HFD-fed mice. This finding led us to investigate the role of CP1 in hyperlipidemia and atherosclerosis *in vivo*. Interestingly, serum total cholesterol levels showed a significant increase by approximately 23% and 30% and en face analyses of total aorta surfaces revealed increased atherosclerotic lesion area by approximately 2.2-fold and 1.4-fold, respectively in *Ldlr*$^{-/-}$*CP1*$^{-/-}$ female and male mice as compared with *Ldlr*$^{-/-}$ mice. Consistent with to *CP1*$^{-/-}$ results, *Ldlr*$^{-/-}$*CP1* tg mice had reduced serum total cholesterol levels by approximately 29% and 19% with decreased cholesterol in the VLDL fraction, concomitant with reduced serum apolipoprotein B level and also developed reduced total enface aortic lesion area by approximately 19% and 29%, respectively in *Ldlr*$^{-/-}$*CP1* tg female and male mice as compared with *Ldlr*$^{-/-}$ mice.

Conclusion Taken together, CP1 is an atheroprotective adipokine that may offer novel therapeutic strategies to combat hypercholesterolemia and atherosclerosis.

ICAO2013-110

HS-1793, A RECENTLY DEVELOPED RESVERATROL ANALOGUE PROTECTS RAT HEART AGAINST HYPOXIA/REOXYGENATION INJURY VIA ATTENUATING MITOCHONDRIAL DAMAGE

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Objective Resveratrol is known to exert a cardioprotective effect against hypoxia/reoxygenation (H/R) injury. HS-1793 is a novel, more stable resveratrol analog, but its cardioprotective effects were unknown. The present study aimed to test the cardioprotective effect of HS-1793 against H/R injury.

Methods We investigate the role of mitochondria in Sprague Dawley rat heart damage using an ex vivo Langendorff system. Mitochondrial function was determined by measuring mitochondrial oxygen consumption rates. To understand the underlying mechanism of HS-1793-mediated mitochondrial protection, we further tested its effect on two important mitochondrial factors, mitochondrial ROS and calcium flux, both of which damage mitochondria during H/R. We employed MitoSOX red and Rhod 2AM to investigate mitochondrial levels of superoxide (O^{2-}) and Ca^{2+}.

Results HS-1793 ameliorated H/R-induced mitochondrial dysfunction by reducing mitochondrial reactive oxygen species production, improving mitochondrial oxygen consumption and suppressing mitochondrial calcium (Ca^{2+}) overload during reperfusion. Moreover, HS-1793-treated rat heart showed reduced infarct size.

Conclusion HS-1793 has therapeutic potential against H/R injury. The cardioprotective effects may be related to its ability to reduce mitochondrial ROS formation and Ca^{2+} overload. However, more extensive investigation will be required to elucidate the underlying molecular mechanisms of HS-1793 on attenuating reoxygenation injury. The newly described role of HS-1793 may provide new insight into developing new drugs or synthesizing new resveratrol analog for cardioprotection.

ICAO2013-121

BIDIRECTIONAL ROLE OF CGMP IN CARDIAC CELL PROTECTION

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Objective Cyclic guanosine 3,5-monophosphate (cGMP) is a second messenger molecule, and the cGMP/Protein kinase G (PKG) signaling pathway is involved in the cardioprotective mechanism underlying ischemic preconditioning and postconditioning. We aimed to determine if cGMP could modulate mPTP opening by inhibiting glycogen synthase kinase 3 beta (GSK3 beta) through PKG. We then investigated the if cGMP is involved in inhibitory action on Akt.

Methods H9c2 cells, rat cardiomyoblast, were treated with Br-cGMP (500 microM) and then immunobloting and protein phosphatase 2A (PP2A) activity assays were performed. After transfection with GSK3 beta mutant DNA or PKG Ialpha siRNA, immunoblotting and immunoprecipitation were also performed.

Results cGMP inactivated GSK3 beta through PKG (this leads to acute cardioprotection). In addition, the negative regulatory effect of cGMP on Akt activity (this may lead to prevention of hypertrophy and heart fialure, and the regulation of NO synthesis) is not mediated by PKG but may be through the up-regulation of PP2A activity.

Conclusion We propose that cGMP is a versatile signal with dual beneficial role in cardiac cell survival.

CMR eJOURNAL Official Journal of the International Chair on Cardiometabolic Risk

ICAO2013-141

FISH OIL PREVENTS EXCCESIVE BODY WEIGHT GAIN CAUSED BY AN ADVERSE EFFECT OF PIOGLITAZONE TREATMENT IN KK MICE

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Objective Pioglitazone, one of thiazolidinediones (TZDs) which are potent and selective ligands for peroxisome proliferator-activated receptor gamma (PPARγ), have been used widely in clinical treatment of type 2 diabetes as insulin-sensitizer drugs. However, the body weight gain has been frequently observed in TZDs treatment-patients with type 2 diabetes. Fish oil improves lipid metabolism and obesity by suppressing fatty acid synthesis and stimulating fatty acid oxidation in the liver. In this study, we demonstrated that the combination of pioglitazone and fish oil suppressed the weight gain by pioglitazone in 2 diabetes status KK mice.

Methods Male KK mice aged at 7 weeks were fed experimental diets for 8weeks. The experimental diets were consisted of 20 energy % (en%) fat. SO, SP/L and SP/H diets contained 20 en% safflower oil with 0%, 0.006% or 0.012% pioglitazone. FO, FP/L, FP/H diets were replaced fat source with 10 en% fish oil and 10 en% safflower oil mixture.

Results Body weight gains were significantly higher in SP/L and SP/H groups compared with SO group, but the body weight gains were suppressed by fish oil feeding. The same tendency was also observed on subcutaneous fat mass. The hepatic mRNA expressions of lipogenic enzymes, including FAS, SCD-1 and ACC, were significantly decreased in fish oil-fed groups. Whereas, the hepatic mRNA expressions involved in fatty acid oxidation such as AOX, UCP-2 and MCAD were unaffected by fish oil feeding. Although no significant difference was showed in blood glucose levels, plasma insulin levels were significantly decreased in pioglitazone added groups compared with SO group.

Conclusion The combination of pioglitazone and fish oil decreased accumulation of subcutaneous fat, resulting in suppression of the pioglitazone-induced body weight gain through inhibition of hepatic fatty acid synthesis by fish oil. In addition, pioglitazone lowered plasma insulin levels and improved insulin resistance. These results suggest the combination intake of pioglitazone with fish oil may lower an adverse effect of pioglitazone and exert beneficial effects on glucose metabolism.

ICAO2013-157

ADIPOGENIN, A REGULATORY GENE PLAYS ROLE IN FAT ACCUMULATION OF ADIPOGENESIS

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Objective Adipose tissue plays a central role in the regulation of energy balance, insulin sensitivity, immunological responses, and vascular diseases. Adipogenin, consists of 240 nucleotides specifying a protein of 80 amino acid residues, is one of regulatory factor involved with adipogenesis and fat development. The aim of this study was performed to investigate the functions of adipogenin related to adipogenesis using overexpression of adipogenin gene with fusion protein system and down-regulation of adipogenin gene with shRNA-mediated silencing.

Methods In the overexpression study, we constructed a fusion protein of adipogenin with an epitope tag of GFP using the pcDNA3.1-CT-GFP plasmid vector and transfected into mouse fibroblast C2C12 cells by Lipofectamine 2000. The content of fat accumulation and gene expressions in transfected cells were examined with confocal image system, western blot, Oil Red O and Q-RT-PCR.
To analysis of the gene expression profiles in down-regulated 3T3-L1 cells, the vector-based shRNA against adipogenin were transfected to 3T3-L1 cells using a mouse U6 promoter-based piGENE-mU6 vector. Gene expression profiles between control and sh-adipogenin shRNA transfected cells were examined using microarrays.

Results The transfected adipogenin fusion protein was expressed in C2C12 cells and localized into cytoplasm observed in confocal microscope. Western blot analysis using anti-GFP antibodies showed that transfected adipogenin-GFP fusion protein was expressed in C2C12. Adipogenin-GFP transfectied cells were increased the Oil-red stained cells with adipocyte differentiation medium with or without adipogenic inducer, troglitazone and PPAR-γ2, adipogenic maker gene expressed in C2C12.
However, the silencing of adipogenin gene, transfectant sh-adipogenin-3T3-L1 cells decreased fat accumulation compared with control shRNA-transfected cells. Adipogenesis related genes were decreased in adipogenin knocked-out 3T3-L1 cells such as SREBP, C/EBPα, PPAR-γ2 and GLUT4. To identify adipogenin-regulated targets, 718 down-regulated and 508 up-regulated genes over with two fold changes were identified in 3T3-L1-control and 3T3-L1-sh-adipogenin cells with cDNA microarray analysis.

Conclusion Adipogenin overexpression was shown to increased fat accumulation and adipocyte differentiation. Moreover, the silencing of adipogenin gene has decreased adipocyte differentiation and down-regulated the adipogenic genes expressions. These results indicate that adipogenin is a critical factor for adipose tissue development.

ICAO2013-159
DEFICIENCY OF ADIPOGENIN DECREASES FAT ACCUMULATION AND ALTERS GLUCOSE METABOLISM

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Objective Adipose tissue is a critical role in the peripheral regulation of body homeostasis, specifically, energy intake, storage and expenditure acts as a secretory /endocrine organ that mediates numerous physiological and pathological processes. In a previous reports, adipogenin mRNA is highly expressed in adipose tissue and elevated during adipocyte differentiation. SiRNA mediated a reduction of adipogenin mRNA in 3T3-L1 cells inhibited the process of adipocyte differentiation. The objective of this study is to investigate fat and glucose metabolism using adipogenin KO (ADIG-KO) mice.

Methods ADIG-KO mice were backcrossed to C57BL/6J for 7th generation and fed with normal diet. The body weight was measured from 4 to 15weeks old. Glucose and insulin tolerance test was performed from 20-23 weeks old. At 17weeks old, respiratory quotient and energy expenditure were measured. Gene expressions in adipose and liver tissues of 20 weeks old were analyzed with real-time Q-RT-PCR.

Results The body weight of ADIG-KO mice fed normal diet was significantly lower than that of WT mice, however food intake was not changed among two groups. The ADIG-KO mice exhibited a marked reduction in deposition of WAT compared to WT mice such as subcutaneous, epididymal and perirenal fat pad. In ADIG-KO mice, leptin mRNA in adipose tissue was significantly decreased compared with WT mice. PGC1α mRNA in liver was higher in ADIG-KO mice than in WT mice. In the GTT, ADIG-KO mice showed elevated postinjection glucose level by 57.8% compare with WT mice. In ITT, ADIG-KO mice to be more insulin sensitive compare with WT mice. In ADIG-KO mice, RQ and energy expenditure were higher than WT mice.

Conclusion ADIG-KO mice decreases adipose tissue mass, protects against weight gain, decreased adipogenic gene in adipose tissue and increase gluconeogenesis related gene in liver. In addition, ADIG-KO mice were more insulin sensitive but less glucose tolerant, probably because of lower insulin concentration. It might be possible to speculate that the extent of activation of adipogenin gene affects fat accumulation and glucose homeostasis directly or indirectly.

Physical Activity/Exercise

ICAO2013-022

EFFECT OF PROGRESSIVE RESISTANCE EXERCISE TRAINING (PRT) ON HEPATIC FAT IN ASIAN INDIANS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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Objective NAFLD is closely associated with obesity and insulin resistance. There is paucity of data on the effect of resistance exercise on hepatic fat content. We evaluated the effect of PRT on hepatic fat content, body composition and insulin sensitivity in patients with NAFLD.

Methods This pre-post intervention study included 30 adult patients disgnosed to have fatty liver on ultrasound with alcohol intale <140 gm/week and no secondary cause of fatty liver. Patients underwent thrice weelky sessions (40 minutes each) of resistance exercises including flexion at biceps, triceps, and hip, knee extension and heel rise for 12 weeks. Pre- and post-intervention evaluation included anthropometry, BIA analysis, short insulin tolerance test (SITT), lipid profile and hepatic fat quantification by MRI.

Results Twenty four patients (17 males, 7 females, mean age 39.8±10.5 yrs) completed the study protocol with 78.7% compliance to PRT protocol. There was significant decrease in waist, hip and mid-thigh circumferences and skinfold thicknesses at biceps, triceps, subscapular and suprailiac regions ($p<0.05$), with no significant change in BMI and WHR. Insulin sensitivity improved significantly at 12 weeks as indicated by increase in kvalue on SITT (0.9 vs 1.3, $p=0.002$). A decrease in total and LDL-c with increase in HDL-c was noted after 12 weeks ($p<0.05$). Hepatic fat content also decreased at 12 weeks (22.3±3.9 vs 21.4±4.0 %, $p=0.01$).

Conclusion Moderate intensity PRT is associated with significant improvement in hepatic fat, truncal subcutaneous fat and insulin sensitivity in patients with NAFLD.

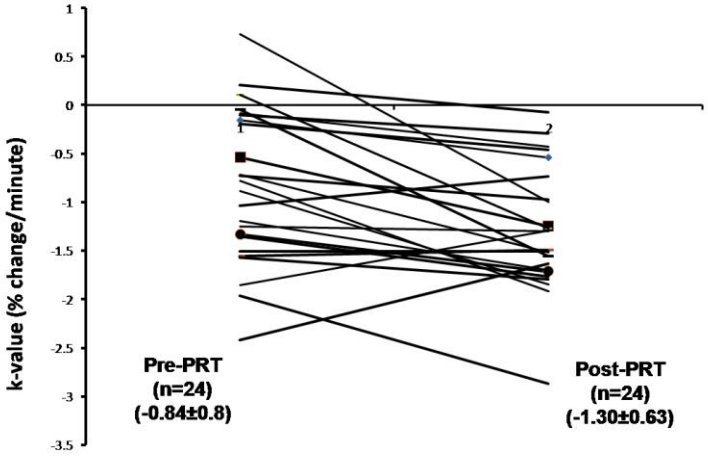

Table 1. Baseline and post-PRT characteristics of the study population

Parameter	Pre-PRT (Baseline, n=24)	Post-PRT (3 months, n=24)	Mean difference (95% CI)	P-value*
Weight (kg)	70.6 ± 8.7	70.3 ± 8.8	0.26 (-0.10, 0.62)	NS
Body mass index (kg/m^2)	26.7 ± 3.7	26.5 ± 3.6	0.10 (-0.03, 0.24)	NS
Systolic blood pressure (mm Hg)	128.1 ± 9.4	126.8 ± 7.0	1.33 (-1.26, 3.93)	NS
Diastolic blood pressure (mm Hg)	80.7 ± 7.0	80.1 ± 7.1	0.58 (-1.27, 2.44)	NS
Circumferences (cm)				
Waist	87.0 ± 8.7	86.3 ± 8.7	0.76 (0.42, 1.10)	<0.001
Hip	96.4 ± 7.7	95.5 ± 7.6	0.93 (0.55, 1.30)	<0.001
Mid-arm	29.6 ± 3.7	28.9 ± 3.5	0.70 (0.42, 0.98)	<0.001
Mid-thigh	53.4 ± 4.4	52.6 ± 4.8	0.83 (0.48, 1.19)	<0.001
Waist-to-hip ratio	0.90 ± 0.06	0.90 ± 0.06	0.004(-0.002, 0.003)	NS
Skinfold thickness (mm)				
Biceps	12.8 ± 3.1	12.4 ± 2.8	0.45 (0.23, 0.67)	<0.001
Triceps	17.5 ± 5.4	16.6 ± 5.4	0.84 (0.65, 1.03)	<0.001
Subscapular	31.3 ± 3.1	30.3 ± 3.2	0.97 (0.70, 1.24)	<0.001
Suprailiac	29.6 ± 3.4	28.5 ± 3.5	1.05 (0.77, 1.33)	<0.001
K_{ITT}	-0.84 ± 0.80	-1.30 ± 0.63	0.45 (0.20, 0.70)	0.002
Fasting blood glucose (mg/dL)	99.8 ± 16.1	99.3 ± 14.0	0.52 (-4.4, 5.43)	NS
Total cholesterol (mg/dL)	174.5 ± 27.4	168.8 ± 24.1	5.72 (0.54, 10.9)	0.03
Low density lipoprotein cholesterol (mg/dL)	112.0 ± 23.2	104.3 ± 19.1	7.68 (2.39, 13.0)	0.006
High density lipoprotein cholesterol (mg/dL)	36.4 ± 7.9	37.4 ± 6.7	-0.98 (-1.7, -0.26)	0.009
Triglycerides (mg/dL)	130.7 ± 45.1	135.6 ± 43.8	-4.9 (-12.3, 2.5)	NS
Total bilirubin (mg/dL)	0.58±0.19	0.50±0.08	0.07(-0.003, 0.15)	NS
Aspartate aminotransferase (IU)	37.0±12.3	37.3±6.8	-0.33(-4.17, 3.50)	NS
Alanine aminotransferase (IU)	43.6±25.1	38.1±9.2	5.46 (-1.89, 12.8)	NS
Alkaline phosphatase (IU)	247.5±86.5	258.8±68.7	-11.3 (-28.6, 5.9)	NS
Body fat by bioimpedance (%)	27.7 ± 8.8	27.0± 8.4	0.72 (0.11, 1.32)	0.02
Hepatic fat by MRI (%)	22.2 ± 3.9	21.3 ± 4.0	0.89 (0.18, 1.6)	0.01

Data are mean ± standard deviation (unless specified); *: comparison of mean difference against zero; K_{ITT}: rate of decline of blood glucose during the short insulin tolerance test; MRI: magnetic resonance imaging; NS: not significant

ICAO2013-137

BENEFICIAL EFFECTS OF EXERCISE ON CARDIAC STRUCTURE AND FUNCTION IN HEARTS OF TYPE 2 DIABETIC RATS: ROLE OF EXERCISE TYPE

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Objective Type 2 diabetes mellitus (T2DM) is caused by insulin resistance and leads to hyperglycemia, hyperlipidemia, and pathological cardiac hypertrophy. The beneficial effects of aerobic and resistance exercises on the cardiac function caused by T2DM are not fully understood. Our study aims to determine the effects of aerobic and resistance exercises on the cardiac and mitochondria functional alterations caused by T2DM in rats.

Methods We divided Otsuka Long-Evans Tokushima fatty (OLETF) rats into three groups; sedentary (SED), aerobic exercise (EXA) and resistance exercise (EXR) rats. We exercised the EXA and EXR rats 5 days/week for 12 weeks by running them on a treadmill and up a ladder at an angle of 85 degrees, respectively. The effect of aerobic or resistance exercise in diabetes was investigated on glucose tolerance tests, lipid profiles, echocardiography and mitochondrial functional study.

Results Both exercise groups significantly improved blood glucose tolerance, and lipid profiles in T2DM, but resistance exercise was more potent for improving the pathological conditions than aerobic exercise was. Both exercise regimes cardiac performance and resistance exercise had greater improvements in ejection fraction and fractional shortening. Mitochondrial Oxygen consumption rate, ROS production and membrane potential were also improved in resistance exercise, although aerobic exercise improved only ROS production.

Conclusion Our results show that both the aerobic and resistance exercises were beneficial to cardiac performance, but the resistance exercise was more potent than the aerobic exercise for improving glucose uptake, cardiac contractility and mitochondrial function than aerobic exercise which may be the one of beneficial therapeutic strategy for the treatment of T2DM.

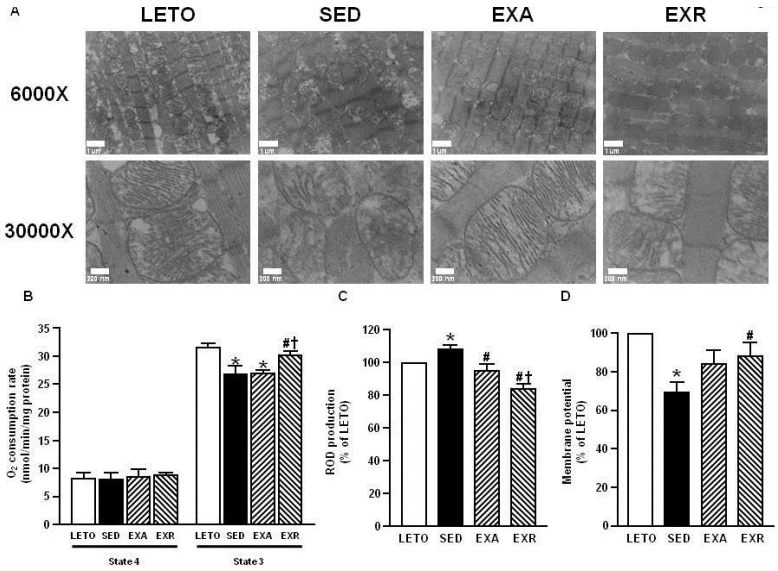

Figure 1. Mitochondrial alteration and functional study. A: electron microscopy. B: oxygen consumption rate. C: ROS production. D: Mitochondrial membrane potential. Data are expressed as mean ± SEM of 3~4 rats per groups. *p<0.05 vs. LETO; #p<0.05 vs. SED, †p<0.05 vs. EXA.

Table 1. Echocardiography results in OLETF rats after 12 weeks exercise.

	LETO (n=6)	SED (n=6)	EXA (n=6)	EXR (n=6)
IVSd (mm)	1.97±0.06	1.91±0.09	1.46±0.05*#	1.37±0.05*#
LVPWd (mm)	1.85±0.06	2.04±0.05*	1.45±0.05*#	1.44±0.05*#
LVIDd (mm)	7.42±0.14	6.66±0.2*	8.18±0.21*#	7.52±0.21*#†
LVIDs (mm)	3.5±0.31	3.14±0.24	3.96±0.25#	2.59±0.17*†
EDV (ml)	0.91±0.05	0.69±0.05*	1.2±0.09*#	1±0.04*#†
ESV (ml)	0.12±0.03	0.09±0.02	0.16±0.03#	0.05±0.01*†
EF (%)	89.05±1.84	87.96±1.74	86.79±1.63	95.38±0.7*#†
FS (%)	53.12±3.59	53.16±2.48	51.76±1.99	65.5±2.1*#†
SV (ml)	0.8±0.03	0.6±0.04*	1.04±0.06*#	0.9±0.06#
CO (ml/min)	396.07±19.91	302.11±19.48	475.63±30.41*#	432.01±23.02#
CO index	0.77±0.05	0.58±0.02*	0.89±0.05#	0.85±0.04#
RWT	0.77±0.05	0.58±0.02*	0.89±0.05*#	0.85±0.04*#

Values are mean ± SEM. Significant difference: *p<0.05 vs. LETO; #p<0.05 vs. SED; †p<0.05 vs. EXA in a one-way ANOVA with Duncan *post hoc* test. SED, sedentary; EXA, aerobic exercise; EXR, resistance exercise; IVSd, intraventricular septum in diastole; LVPWd, left ventricular posterior wall thickness in diastole; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; EDV, end of diastolic volume; ESV, end of systolic volume; EF, ejection fraction; FS, fractional shortening; SV, stroke volume; CO, cardiac output; RWT, relative wall thickness.

ICAO2013-166

TARGETING CARDIORESPIRATORY FITNESS TO IMPROVE CARDIOMETABOLIC RISK PROFILE AND ATHEROSCLEROSIS PLAQUE PROGRESSION IN POST-CORONARY BYPASS GRAFT PATIENTS

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Objective Cardiorespiratory fitness (CRF) is recognized as a major predictor of cardiovascular disease and is also associated with cardiovascular health. The present pilot study tested the relevance of targeting CRF to improve the cardiometabolic risk (CMR) profile of patients with established coronary artery disease (CAD) who underwent coronary artery bypass graft surgery followed by a 1-year lifestyle modification program (n=50).

Methods Anthropometric measurements, assessment of lipid profile, magnetic resonance imaging of the heart, abdomen and carotid arteries, an oral glucose tolerance test (OGTT) and a maximal treadmill test were performed before and after the intervention. Patients were classified into two subgroups according to the 50th percentile of change in CRF after the intervention.

Results Patients with the most substantial improvement in CRF (≥50thpercentile) also showed significant improvements in all anthropometric parameters and CMR variables as reflected by decreases in their BMI (Δ=-1.3 kg/m^2,$p<0.01$), waist circumference (Δ=-6.7cm,$p<0.01$), and subcutaneous adipose tissue volume (Δ=-17%, $p<0.01$) as well as in their epicardial (Δ=-27%, $p<0.01$) and pericardial (Δ=-48%, $p<0.01$) adipose tissue volumes. They also significantly reduced their 2h plasma glucose and insulin levels as well as their glucose and insulin areas under the curve measured during the OGTT, decreased their triglyceride and C-reactive protein concentrations and increased their HDL-C and apolipoprotein A1 levels ($p<0.01$). Patients who showed the most important improvement in CRF were those who significantly decreased their right and left carotid artery wall volumes normalized to total vessel volume ($p<0.05$), while no significant change was observed in the subgroup with less improvement in CRF (<50th percentile). The former group of patients also decreased their resting heart rate by 8 beats per minute ($p<0.0001$) while left ventricular end-diastolic mass (+3.8g/m^2, $p<0.01$) and volume (+7.7ml/m^2, $p<0.01$) were increased. Patients with substantial CRF improvements also significantly increased their left ventricular stroke volume (+6.0ml/m^2, $p<0.01$). No such change was observed in the group with less improvement in CRF.

Conclusion Improvement of CRF appears to be an important target to improve cardiometabolic risk, atherosclerosis progression as well as cardiac structure/function in patients with established CAD.

ICAO2013-173
AGED GARLIC EXTRACT IMPROVES ON METABOLIC PARAMETERS IN EXERCISE TRAINED OBESE RATS

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Objective Aged garlic extract (AGE) is known to have a protective effect against immune system, endothelial function, oxidative stress and inflammation. We examined the effects of exercise with and without aged garlic extract administration on body weigh obese rats.

Methods Forty-five Sprague-Dawley rats were fed either a HFD (HFD, n = 40) or a normal diet (ND, n = 5) for 6 weeks and thereafter randomized into ND (n = 5), HFD (n = 10), HFD with AGE (n = 10), HFD with Exercise (n = 10), or HFD with Exercise+AGE (n = 10) for 4 weeks. AGE groups were administered at a dose of 2.86 g/kg·body weight, orally. Exercise consisted of running 15-60 min 5 days/week with gradually increasing intensity.

Results AGE ($P < 0.01$), Exercise, and Exercise+AGE ($P < 0.001$) attenuated body weight gain and food efficiency ratio compared to HFD. Visceral fat and liver weight gain were attenuated ($P < 0.05$) with all three interventions with a greater effect on visceral fat in the Exercise+AGE than AGE ($P < 0.001$). In reducing visceral fat ($P < 0.001$), epididymal fat ($P < 0.01$) and liver weight ($P < 0.001$), Exercise+AGE was effective, but exercise showed a stronger suppressive effect than AGE. Exercise+AGE showed further additive effects on reducing visceral fat and liver weight ($P < 0.001$). AGE significantly attenuated the increase in total cholesterol and low-density lipoprotein-cholesterol compared with HFD ($P < 0.05$). Exercise+AGE attenuated the increase in triglycerides compared with HFD ($P < 0.05$). Exercise group significantly decrease in C-reactive protein ($P < 0.001$).

Conclusion These results suggest that AGE supplementation and exercise alone have anti-obesity, cholesterol lowering, and anti-inflammatory effects, but the combined intervention is more effective in reducing weight gain and triglycerides levels than either intervention alone.

Prevention

ICAO2013-029

BOWEL FREQUENCY AND FOOD INTAKE FREQUENCY

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Objective With regard to bowel movements, in addition to examining the conditions of taking meals in terms of the frequency of food intake, the conditions of living in terms of the times of day of going to sleep and waking up, and the duration of sleep, as well as the physical conditions upon waking up, were also examined and the associations among bowel habits, pattern of living and food intake were studied in order to understand the issues in the management of the health of students.

Methods The subjects of the survey were 373 male and 590 female college students, and a survey of their bowel movements, meal-related factors and lifestyle were surveyed by the questionnaire method.Scores for bowel movements were obtained by examining eight items related to conditions of bowel movement using the Japanese version of the Constipation Assessment Scale, as the bowel score (CAS-J).In addition, with regard to meal-related factors, an attempt was made to understand the actual conditions of the dietary habits of the students by surveying the conditions of food intake with regard to ten items of food groups and whether or not there is intake of breakfast.

Results With regard to the frequency of food intake, CAS-J was low, for male students, in cases of high frequency of intake of fish and meat. On the other hand, for female students, CAS-J was significantly high, particularly in cases of almost no intake of fruit, eggs, meat, tofu, pulse, seaweed and soft drinks. With regard to intake of breakfast, CAS-J was significantly low for female students who “eat every day”. With regard to the status of waking upon waking up, values were low for “quite awake”, and significant differences were found with “not very awake”, for both male and female students.

Conclusion From the foregoing results, it was shown that meal-related factors and the life pattern of sleep and wakefulness, as well as the physical conditions upon waking up, are related to CAS-J.

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ICAO2013-055

TIME-BASED CHANGES IN BODY COMPOSITION AND BONE DENSITY IN FEMALE HIGH SCHOOL TRACK AND FIELD ATHLETES

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Objective It is important that medical and scientific support for younger athletes be based on not only on improvement of athletic performance but also the creation of a healthy foundation for the future. Bone density increases with secondary sexual characteristics, reaches a peak by age 17 to 18, and then subsequently decreases. However, long-distance runners are known to tend to have low bone density, and there are many aspects of the effects of routine, strenuous training on growth that remain unknown. Therefore, this study was conducted for the purpose of obtaining basic information for effectively providing medical and scientific support.

Methods Body measurements, site-specific bone density of the entire body, arms, legs and trunk by DXA, body fat percentage(%fat) , body fat, and lean body mass(LBM) were measured in female high school long distance runners residing in O prefecture in Japan for the three year period from 2010 to 2012. Biochemical tests(blood, urine) and a survey of nutrition and eating habits were performed simultaneously.

Results (1)Although height, weight, BMI and waist circumference were examined, there were no significant changes observed between measurement years.
(2)There were no significant changes observed in systemic body fat percentage or systemic lean body mass between measurement years. As a result of examining correlations between measurement parameters, a correlation was observed between systemic lean body mass and bone density (r=0.658). Lumbar bone density in 2010 was between 0.678 to 1.073 g/cm^3. In 2011, values were between 0.741 to 1.082 g/cm^3. In 2012, values were between 0.736 to 1.077 g/cm^3. Bone densities were lower when compared with others of the same age.

Conclusion Although the subjects consisted of athletes on a team that was competitive even on a national level, their bone densities were low and they were found to be at risk for osteoporosis in the future.
Bone metabolism markers such as urine NTX and blood NTX were also measured, and findings regarding bone density and bone metabolism are currently being examined.
In addition, studies are planned to be conducted in the future regarding the relationship between diet and bone density while focusing particularly on the proportion of carbohydrates in the total amount of ingested energy.

ICAO2013-108

A LOW DOSE OF METFORMIN IN YOGHURT IMPROVES COMPLIANCE AND INCREASES GLUCOSE EFFECTIVENESS IN NORMOGLYCEMIC OBESE PERSONS

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Objective The number of patients suffering from type 2 Diabetes is increasing significantly. Obesity seems to be an important risk factor in this development. It is known that biguanides can be used in de treatment and prevention of type 2 Diabetes. Recent studies have showed that a high dose metformin (≥1700 mg) can reduce the incidence of type 2 Diabetes with 30% after 3 years. However, due to negative side effects such as bad taste and gastro-intestinal complains 30-70% of the patients using metformin were non compliant. It is known yoghurt can reduce these negative side effects. The objective of this study is to investigate the effect of a low dose metformin dissolved in yoghurt on the glucose metabolism and the influence of the combination on taste and compliance.

Methods For this pilot study 45 persons (BMI>26) were included. Inclusion criteria were having a BMI>26 and a waist size of respectively >92cm in men and >82 cm in women. Having type 2 Diabetes, hypertension, recent diet changes, cholesterol >6,5 mmol/l, alcohol abuse and liver or kidney diseases were excluding criteria. Patients were randomized in three groups, 450 mg metformin (n=15), 250 mg metformin (n=15) and a placebo group (n=15). During 6 weeks patients received a yoghurt each morning. The primary setpoint of this study was HbA1c and furthermore, compliance and side-effects (GI side effects) were measured.

Results After 6 weeks the HbA1c of the 450 mg and 250 mg group was decreased borderline significant. (table 1) This is in line with weight loss and waist size reduction. Taste was judged as “good” and compliance was, therefore, high in treatment arms. While in earlier studies compliance in the use of metformin was not sufficient due to side effects, in this study side effects were equally to the placebo group.

Conclusion This study showed that a very low dose of metformin in yoghurt improves the glucose metabolism due to the high compliance. These promising results of this pilot study can be an incentive to do further research in bigger population and longer treatment studies in the future.

Table 1. Study Outcome

	metformin 450 mg	metformin 250 mg	placebo	Kruskal Wallis test
male/female ration	0,2	0,13	0,13	
mean age	47 ±6,5	47 ±9,8	44 ±6,6	
HbA1c change (mmol/mol)	-0,53 (1,4%)	-1,5 (4,0%)	0	P<0,05
Waist size (cm change)	-2,3	-2,4	-0,6	p=0,322
BMI % change	-0,26	-0,25	+0,03	p=0,506
Good taste	86%	85%	84%	
GI complains	20%	20%	30%	

ICAO2013-163
SELF-REPORTED WAIST CIRCUMFERENCE FOR CLASSIFYING CHILDREN WITH CARDIOVASCULAR RISK

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Objective The objectives of this study were two-fold, (1) to validate the self-reported waist circumference (SRWC) against assessor measured waist circumference (MWC) and (2) to evaluate the accuracy of SRWC in classifying children (i) with cardiometabolic risk factors (CMRFs) clustering and (ii) overweight/obese status.

Methods A cross-sectional cluster random sample aged 6-18 years with the self-reported body weight (BW) and height (BH) and waist circumference (WC) were used for data analysis. Children were given a self-administrated questionnaire including questions of demographic data and anthropometric values to bring home for completion. They were asked to return the questionnaire and fast themselves for at least 8 hours on the day of the survey. Anthropometric measures and blood pressure were taken by trained research staff. Fasting blood samples were collected for the measurement of fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol.

Results A total of 515 boys and 711 girls who had self-reported waist circumference data were eligible to enter data analysis. The agreement between SRWC and MWC was assessed by intra-class correlation coefficient (ICC) and it ranged from 0.77 to 0.87. The SRWC values to classify children with a clustering of CMRFs exhibited moderate to moderately high sensitivity (95% CI) [68%(0.43-0.87) for boys and 84%(0.60-0.97) for girls] and specificity [70%(0.66-0.74) for boys and 72%(0.68-0.75) for girls]. The area under the receiver operating characteristics [AUC-ROCs (95% CI)] ranged from acceptable to excellent [from 0.76(0.68-0.84) for boys to 0.83(0.76-0.90) for girls] in classifying children with a clustering of CMRFs.
The SRWC values to classify overweight/obesity children showed moderately high sensitivity [74%(0.66-0.81) for boys and 77%(0.69-0.84) for girls] and specificity [78%(0.74-0.82) for boys and 82%(0.79-0.85) for girls]. The AUC-ROCs (95% CI) ranged from acceptable to excellent [from 0.84(0.80-0.88) to 0.84(0.79-0.88)] in classifying children with a clustering of CMRFs and overweight/obesity.

Conclusion SRWC shows high validity to detect MWC and could be used as a screening tool for classifying children with a clustering of CMRFs and overweight/obesity status in Hong Kong Chinese children.

ICAO2013-169

TARGETING WAIST AND CARDIORESPIRATORY FITNESS TO REDUCE RISK OF DEVELOPING DIABETES AT THE WORKPLACE: RESULTS FROM THE GRAND DÉFI ENTREPRISE

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Objective Our poor lifestyle habits leading to the current epidemic of metabolic syndrome and diabetes have changed the mosaic of modifiable risk factors. While most abdominally obese individuals fail to adopt healthy behaviours over the long term, few cardiometabolic health programs are offered in the workplace.

Methods About 600 employees from four companies were involved in a pilot project of the "Grand Défi Entreprise" (Great Corporate Challenge), which involved a 3-month friendly in-house competition among employees to improve their lifestyle habits. For that purpose, a comprehensive health assessment provided by a mobile risk assessment unit before and after the 3-month challenge was performed. Glycated hemoglobin (HbA1c) was measured at the laboratory on frozen sample to identify the average plasma glucose concentration over the last 2 to 3 months. Employees were classified as normoglycemic, impaired glycemic (IGT) or type-2 diabetic in regards of their levels of HbA1c (<5.7%, between 5.7% ad 6.4%, ≥6.5%, respectively).

Results More than half of the sample (51%) were IGT. After the 3-month contest, waist circumference (WC) was significantly reduced (-4.4±3.9 cm, $p < 0.0001$). Cardiorespiratory fitness (CRF) was improved as indicated by a significantly reduced heart rate assessed at a standardized submaximal workload on a treadmill (3.5mph at 2% slope) ($p < 0.0001$). Results show that the IGT individuals reduced significantly their HbA1c (5.9±0.02% vs 5.79±0.03%, before and after intervention). The IGT group benefit most from their lifestyle modification in reducing their cardiometabolic risk profile (HDL-C=+0.04±0.18 mmol/L; TG=-0.42±0.18 mmol/L; $p < 0.0001$, etc.). Interestingly, WC explain 9.8% of the variance in baseline HbA1c whereas CRF and WC significantly explain changes in HbA1c ($p < 0.01$).

Conclusion Results from this pilot intervention study conducted at the workplace provide evidence that targeting both WC and CRF is relevant to reduce risk to develop diabetes and cardiometabolic risk factors of workforce.

ICAO2013-170

INHIBITION OF NEOINTIMAL HYPERPLASIA BY EPOTHILONES THROUGH P53-DEPENDENT APOPTOSIS OF ARTERIAL SMOOTH MUSCLE CELLS

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Objective In several studies, microtubule stabilizing agents (MTSAs), such as, paclitaxel have been found to interfere with vascular smooth muscle cell (VSMC) migration and proliferation in vitro. In vivo, MTSA have also been found to inhibit neointimal hyperplasia in a carotid artery endothelial denudation injury model.

Methods In the present study, we investigated the effect of epothilone (EPO), a novel synthesized MTSA, on platelet derived growth factor (PDGF)-BB-induced VSMC proliferation and on balloon-injury-induced neointimal hyperplasia in a rat model, and then subsequently investigated the induction of apoptosis and role of p53 in this process.

Results EPO-B and EPO-D (1-100 nM) effectively inhibited PDGF-BB-induced VSMC proliferation. Treatment with these EPOs (20 μg/rat) also potently reduced balloon-injury-induced neointimal hyperplasia in the rat carotid artery, and potently induced the apoptosis of VSMCs in vitro and in vivo. EPOs also potently induced p53 nuclear accumulation, and the anti-proliferative effects of EPOs were reduced by the p53 inhibitor and by knock down with p53 siRNA. Further study, showed that the p53-regulatory apoptotic proteins Bax and caspase-3 were concomitantly activated by EPO treatment in cultured VSMCs, and treatment with p53 inhibitor attenuated the EPO-induced activation of caspase-3. Moreover, p53 and caspase-3 expressing cells number were concomitantly and significantly elevated in the neointimal hyperplasic areas of EPO-treated rat carotid arteries.

Conclusion These results suggest that the molecular mechanisms underlying the anti-proliferative and anti-neointimal hyperplasia effects of EPOs are due to the apoptotic cell deaths of hyper-proliferated VSMCs via the activation of the p53-dependent caspase-3 pathway.

Smoking

ICAO2013-115

SMOKERS' LIPOPROTEINS EXHIBIT MORE ATHEROGENIC PROPERTIES WITH EMBRYO TOXICITY IN ZEBRAFISH

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Objective There has been limited information about the influence of smoking on lipoprotein properties, particularly in young and moderate smokers who had been smoking fewer than 10 cigarettes per day for 3 years.

Methods To investigate the biochemical features of lipoproteins from male smokers (n = 16, 24 ± 1 years old), we compared their lipoprotein profiles with those of a control group (n = 15, 24 ± 1 years old).

Results All lipoprotein particles from the smoking group had a higher extent of oxidation and glycation with higher triglyceride content than those in the control group. The LDL from smokers was more sensitive to oxidation and promoted more foam cell formation in macrophages. HDL from smokers showed impaired antioxidant ability and with increase of triacylglycerol content than that of the non-smoker group. However, CETP activities were greatly enhanced in the HDL fractions by the moderate smoking. All of these modified properties of lipoproteins, including oxidation and glycation, are closely linked to the lower antioxidant ability and elevated inflammatory parameters in young smokers.

Conclusion Smoking at a young age, despite of moderate extent, could impair the beneficial functions of HDL to facilitate atherogenic progress.

Steroid Hormones

ICAO2013-120
THE RAPID ACTION OF CORTISOL ON CARDIAC CONTRACTILITY: ACTIVATION OF PKC AND OUABAIN-INHIBITED NA+/K+ ATPASE

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Objective Although the immunological functions and hypertensive effect of the adrenal stress hormone cortisol are well known, the direct physiological effect of cortisol on heart function is still unknown.

Methods Thus we tested the rapid actions of cortisol on rat heart hemodynamics using *ex vivo* Langendorff system, confocal microscopy and immunoblotting method.

Results Cortisol(10 microM) perfusion did not produce significant changes in heart rate ($p>0.05$, $n=10$) but coronary flow and left ventricular developing pressure (LVDP) were significantly decreased ($P<0.05$). The administration of cortisol on isolated rat heart increased the phsophorylation of protein kinase C (PKC) delta, and the decrease in LVDP by cortisol treament was significantly attenuated in the presence of a PKC peptide inhibitor. Ouabain is a specific inhibitor for Na+/K+ ATPase and thereby increases intracellular calcium contents. In cardiomyocytes, Ouabain-induced increases in both cytoslolic and mitochondrial calcium were significantly suppressed. Cortisol can rapidly phosphorylate both ser23 and Tyr10 sites of Na+/K+ ATpase, whcih increases its pumping activity.

Conclusion Taken Together, cortisol may rapidly influence heart contractility through the activation of PKC and Na+/K+ ATPase, which can lead to the suppression of calcium handling in heart.

Treatment

ICAO2013-023

COMBINATION THERAPY HAS ADDITIVE EFFECTS TO SIMULTANEOUSLY IMPROVE VASCULAR AND METABOLIC PHENOTYPES OVER MONOTHERAPY IN PATIENTS WITH HYPERCHOLESTEROLEMIA

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Objective We evaluated simultaneous vascular and metabolic responses to pravastatin and valsartan therapy, alone or in combination, in hypercholesterolemic patients.

Methods Forty-eight hypercholesterolemic patients (23 had metabolic syndrome) were given pravastatin 40 mg and placebo, pravastatin 40 mg and valsartan 160 mg, or valsartan 160 mg and placebo daily during each 2 month treatment period in a randomized, single-blind, placebo-controlled cross-over trial with three treatment arms and two washout periods (each 2 months).

Results When compared with baseline, all three treatment arms improved endothelial dysfunction as assessed by brachial artery flow-mediated dilation (FMD). Of note, FMD improved to a greater extent with combined therapy vs. either monotherapy (P<0.001 by ANOVA). Interestingly, when compared with monotherapy, combined therapy significantly reduced hs-CRP levels to a greater extent (P=0.019 by ANOVA on Ranks). We also observed simultaneous improvement in metabolic phenotypes with all three treatments causing increased plasma adiponectin levels, reduced fasting plasma insulin levels, and increased insulin sensitivity (determined by QUICKI) relative to baseline measurements. For the first time in a statin combination trial, pravastatin combined with valsartan therapy increased plasma adiponectin, lowered fasting insulin, and improved insulin sensitivity in an additive manner when compared with either monotherapy alone (P=0.003, P=0.049, and P=0.049 by ANOVA on Ranks, respectively). Overall, we observed similar results in 23 patients with metabolic syndrome.

Conclusion Pravastatin combined with valsartan improved endothelial function and metabolic phenotypes in an additive fashion in patients with hypercholesterolemia or metabolic syndrome.

ICAO2013-107

STABILITY AND LONG STORAGE LIFE OF A SMALL DOSE OF METFORMIN IN YOGHURT

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Objective As diabetes mellitus type 2 is becoming a worldwide epidemic, the use of metformin increases. Unfortunately, metformin is known to have reasonable side effects such as gastro-intestinal complains and metal taste which can influence the compliance. Therefore it can be usefull to determine more compliant methods to use metformin. It is known youghurt can reduce gastro-intestinal complains and as metformin is soluble in yoghurt, the aim for this research is to investigate the stability and sterility of metformin in yoghurt. The combination of these two products will influence taste and compliance.

Methods Yoghurt was mixed with 250 mg or 450 mg metformin. Metformin speculums were determined by HPLC/UV in room temperature (KT) and in 4C (KK). In order to statistically account for the non-perish-ability, per measuring station 3 bottles were checked for analysis. All yoghurt products with 250 mg and 450 mg metformin were made at one day in a pilot plant under food grade circumstances and with food grade ingredients. As control group yoghurt with placebo was used. Stability tests were done on day 0, 7, 14, 21, 28 and 35 and PH values were also determined. Sterility tests were done on days 1, 7, 90 and 180 days .

Results During determination of the stability of metformine dissolved in yoghurt, metformine concentration appeared to be highly stable and independent of temperature.
Sterility of the mixture was also proven after storage of 180 days in a temperature of 4 C, as by testing no microbiological contamination was found. It can be concluded that metformine dissolved in yoghurt is very stable and non perishable for a long time. (table 1)

Conclusion Our results seem to implicate dissolving metformin in yoghurt is a safe and new solution to deal with the side effects of metformin. If taken daily, the metformin-yoghurt enables patients with diabetes type 2 or persons with high risk of developing diabetes type 2 to take metformin as a part of the meal. Metformin in yoghurt can decrease the side effects and therefore improve the compliance. In the future more clinical research for patient compliance, taste and side effects has to be done.

	Day 0	Day 7	Day14	Day 21	Day 28	Day 35
Placebo KK	<1	<1	<1	<1	<1	<1
Placebo KT	<1	<1	<1	<1	<1	<1
Metf. 250 mg KK	90,5	90,6	92	91,8	93	92,2
Metf. 250 mg KT		95,3	94,3	93,6	92,3	
Metf. 450 mg KK	86,6	85,7	88	88,6	86	86,8
Metf. 450 mg KT		86,9	89,6	89,1	87,7	

ICAO2013-125

EFFECT OF 'ITRIFAL SAGHIR'ON ABDOMINAL OBESITY: A RANDOMIZED CONTROLLED TRIAL

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Objective Obesity is recognized as an important metabolic disorder and a major public health issue affecting a large number of people around the world. When conventional medicine fails to treat chronic diseases efficaciously and without adverse events, many people seek unconventional therapies including herbal medicine. One of these traditional products, ItrifalSaghir is a polyherbal preparation that has been marketed in Iran for a several years. It is composed of the three medicinal fruits Phyllanthusemblica L. or EmblicaofficinalisGaertn. (Euphorbiaceae), Terminaliachebula Retz.(Combretaceae), and Terminaliabelerica Retz. (Combretaceae); and formulated for the treatment and management of obesity. This study aims to evaluate the waist circumference reducing effectsin healthy adult subjects with a typical Iranian diet.

Methods Using a parallel design, this research was a prospective, two-arm, randomized, double-blind, placebo-controlled study. Sixty-two patients were randomly divided into two groups: placebo (n = 31) and treated (n = 31). For Three months, patients received every day, either 10g of Itrifal Saghiror or 10g of placebo. During the 12-week treatment period, measures of waist circumference (WC) and hip circumference (HC) were assessed at baseline and then once every four weeks. Subjects were selected according to age (16–60 years) and body mass index (BMI) (30–50kg/m2).

Results Results The comparison of mean differences between groups, after 12 weeks of treatment, indicated a significant decline in waist and hip circumferences (ρ <0.001). Nevertheless, no significant difference was observed in the placebo group. Moreover, the mean difference of effective waist circumference decrease was 4.01cm (CI 95% 2.13 - 5.90, ρ < 0.001), and the mean decrease in hip circumference was 3.20cm (CI 95% 1.96 - 4.45, ρ<0.001).

Conclusion The Itrifal Saghir caused a significant improvement in the waist and hip circumferences.

ICAO2013-158

A PRECLINICAL CANDIDATE, DBPR211, TARGETING PERIPHERAL CB1 RECEPTORS IN TREATING TYPE 2 DIABETES

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Objective Type 2 diabetes (T2D) is a multifactorial metabolic disease and its prevalence has reached epidemic proportions. With the increasing prevalence of obesity, the number suffering from T2D, a comorbidity of obesity, is expected to be even higher. Thus, developing new anti-diabetes pharmacotherapeutics is still an urgent medical need. Cannabinoid receptor 1 (CB1) plays an important role in appetite control and glucose and lipid metabolism. To limit the adverse psychological effects resulting from blockade of central CB1 receptor, discovery of peripheral CB1 antagonists in treating metabolic disorders is actively pursued.

Methods Rational design of compounds focusing on the peripheral chemical modifications was undertaken with subsequent lead optimization. *In vitro* assays to evaluate compound activity and binding affinity were established. *In vivo* property of compounds was evaluated by pharmacokinetic studies. The central effects of compounds were examined by the brain to the plasma (B/P) ratio and the capability in reversing CP55940-induced hypothermia and analgesia responses. *In vivo* efficacy was determined by disease animal models including diet-induced obese (DIO) mouse model and the *db/db* diabetic model.

Results DBPR211 (CB1 IC_{50} = 3.4 nM) is orally active and its B/P ratio at 2h after acute dosing (20 mg/kg) to C57BL6/J mice is less than 2%. In addition to its limited brain penetration, it did not reverse CP55940-induced hepothermia and analgesia even at a dose as high as 100 mg/kg. These results strongly support the peripheral selectivity of DBPR211. Chronic treatment of DBPR211 in diet-induced obese mice substantially reduced adiposity and hepatic steatosis and improved glucose intolerance at 10 mg/kg. More encouragingly, the amount of DBPR211 detected in the brain was minimal. The study in *db/db* mice also demonstrates its efficacy in improving insulin resistance.

Conclusion DBPR211 is a potent and orally active peripheral CB1 antagonist with limited brain penetration. Its *in vivo* efficacy supports the therapeutic potential of this second generation of CB1 antagonists in the treatment of type 2 diabetes with additional benefit in weight loss and reduction of liver steatosis. The preclinical studies of DBPR211 is ongoing.

Index

K

L

M

N

O

P

R

S

T

The reference website

on abdominal obesity and related cardiometabolic risk

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