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Objective: Although epidemiological studies have linked adipose inflammation with obesity, the underlying mechanisms are incomplete. It is widely accepted that the interaction between insulin target cells and pro-inflammatory cytokines from accumulated macrophages is a cause of insulin resistance. Reduced mitochondrial capacity has been confirmed in patients with type 2 diabetes, and generally disposes macrophages toward a pro-inflammatory phenotype. However, little is known about decreased mitochondrial function and its effects on secreted macrophage factors which regulate macrophage polarization.

Design and method: To find out the soluble factors of macrophages in adipose inflammation, we have sought six transcriptomes from control macrophages and macrophages that were treated with rosiglitazone. We identified a secretory factor, GDF15, which is required for increased oxidative metabolism in M2-like macrophages stimulated with IL-4 and the PPARg agonist, rosiglitazone.

Results: Administration of GDF15 increased the oxidative function of macrophages, leading to their polarization into an M2-like phenotype, and reversed insulin resistance in ob/ob mice and in HFD-fed mice harboring myeloid-specific deletion of Crif1.
Reintroduction of GDF15-null macrophages into HFD-fed mice in which macrophages were depleted with clodronate treatment rendered them glucose intolerant. Moreover, GDF15 deficiency prevented improvement of insulin sensitivity in mice treated with the Th2 cytokine IL-4.

Conclusions: Thus, GDF15 is an important microenvironmental factor regulating phenotypic polarization of macrophages linked to improvement of systemic insulin resistance.

REDUCING CARDIOVASCULAR RISK IN PATIENTS WITH MORBID OBESITY AFTER BARIATRIC SURGERY

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Objective: The rate of obesity is rising logarithmically, especially morbid obesity (BMI > 40 kg/m ²). Obesity is commonly associated with multiple conditions imparting adverse cardiovascular risk including, hypertension, dyslipidemia and diabetes. Severe obesity is generally refractory to lifestyle modification, including diet, exercise and pharmacological treatment.
The main objective of the study is to confirm the use of bariatric surgery as a means to reduce cardiovascular risk in severely obese patients.

Design and method: We examined 164 patients with morbid obesity (BMI > 40 kg/m ²), they formed two groups. The first group included 81 patients who treated with diet, physical activity and drugs. The second group included 83 patients who using bariatric surgery (gastric bypass). Patients were examined before and after 6 months of treatment. All patients underwent clinical examination, determination of anthropometric parameters, measurement office SBP and DBP, daily monitoring of blood pressure, echocardiography, exploration indicators carbohydrate and lipid metabolism, definition cardiovascular risk with using scales SCORE, PROCAM, DRS, FRAMINGHAM.

Results: It was found that after 6 months of treatment weight loss was observed in both groups. A more significant decrease in body weight was observed in patients after surgical treatment (in first group by 4.6%, in the second group by 22.8%). Weight loss in patients after surgical treatment was associated with a greater decrease in blood pressure, improvement in the daily BP profile, changes in the structural and functional characteristics of the myocardium, decrease in the number of patients with LV hypertrophy, decrease LDL cholesterol, TG, glucose level, which was accompanied by a decrease in the number of patients with glucose intolerance (by 41.2%) and with diabetes (by 75%). Weight loss was associated with reducing the number of patients at very high risk on a scale SCORE by 78%, on a scale PROCAM by 100%, on a scale FRAMINGHAM by 95,6% and on a scale DRS by 13% in patients after surgical treatment.

Conclusions: Weight loss with the use of bariatric surgery contributes to the normalization of BP, reduces LV hypertrophy, has a positive effect on the lipid, carbohydrates profile and reduces cardiovascular risk.

RISK OF DEVELOPING TYPE 2 DIABETES ACCORDING TO BLOOD PRESSURE LEVELS AND PRESENCE OR ABSENCE OF HYPERTENSIVE TREATMENT: THE SAKU STUDY

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Objective: To investigate the risk of developing type 2 diabetes according to blood pressure (BP) levels and presence or absence of hypertensive treatment.

Design and method: Methods:This 5-year cohort study comprised 3,508 Japanese adults aged 30–74 years without diabetes who had undergone a medical checkup including a 75-g oral glucose tolerance test between April 2008 and March 2009 at Saku Central Hospital. Participants receiving antihypertensive treatment were categorized into controlled hypertension (<140/90 mmHg) or uncontrolled hypertension (140/90 mmHg or higher) groups. Participants not receiving antihypertensive treatment were categorized according to the definition of the Japan Society of Hypertension: optimal BP (less than 120/80 mmHg), normal BP (120–129/80–84 mmHg), high-normal BP (130–139/85–89 mmHg), grade I hypertension (140–159/90–99 mmHg) and grade II/III hypertension (160/100 mmHg or higher). Hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of type 2 diabetes as defined by the 75-g oral glucose tolerance test were estimated using multivariable-adjusted Cox proportional hazard models in reference to optimal BP.

Results: During the follow-up, 295 participants developed type 2 diabetes. Those with high-normal BP, grade I hypertension, grade II/III hypertension and uncontrolled hypertension were at significantly higher risk for developing type 2 diabetes, with HRs (95% CIs) of 1.53 (1.03–2.29), 1.53 (1.02–2.32), 2.19 (1.01–4.77) and 1.81 (1.10–2.99), respectively.

Conclusions: Conclusion: Compared with those with optimal BP, individuals with BP 130/85 mmHg or higher not receiving antihypertensive treatment and uncontrolled hypertensives with BP 140/90 mmHg or higher receiving antihypertensive treatment were at a significantly higher risk for developing type 2 diabetes.

THE INFLUENCE OF PREHYPERTENSION, HYPERTENSION AND HBA1C ON THE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS IN PREDIABETES: THE KOREAN GENOME AND EPIDEMIOLOGY STUDY (KOGES)

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Objective: It has been reported that elevated blood pressure (BP) was significantly associated with the increased risk for type 2 diabetes mellitus (T2DM). However, there is still limited information about the influence of BP on the risk for T2DM across the level of glycated hemoglobin (HbA1c).

Design and method: In a cohort of the Korean Genome and Epidemiology Study (KoGES), 2,830 non-diabetic Korean adults with prediabetes defined by HbA1c level of 5.7 - 6.4% were followed-up for 10 years. Multivariate cox proportional hazards assumption was used to assess the risk for T2DM according to the baseline BP categories (normal, prehypertension and hypertension) and HbA1c level (low: 5.7 - 5.9% and high: 6.0 - 6.4%).

Results: The risk for T2DM significantly increased proportionally to BP categories (adjusted Hazard Ratio (HR); reference in normal BP, 1.32 [1.10 – 1.59] in prehypertension and 1.61 [1.35 – 1.92] in hypertension). Subgroup analysis indicated that individuals with high HbA1c had the higher risk for T2DM than individuals with low HbA1c regardless of BP. Additionally, combined presence of hypertension and high HbA1c had the highest risk for T2DM (adjusted HR: 3.82 [3.00 - 4.87]). In each systolic and diastolic BP level, the risk for T2DM significantly increased from systolic BP > 130 mmHg (adjusted HRs: 1.39 [1.15 – 1.71]) and diastolic BP > 80 mmHg (adjusted HRs: 1.30 [1.07 – 1.58]).

Conclusions: BP and HbA1c may be useful tools in identifying individuals with prediabetes more potentially predisposed to T2DM. Prospective studies should be considered to examine whether controlling BP actually lowers the risk for T2DM.

ASSOCIATION OF VITAMIN D WITH THE COMPONENTS OF THE METABOLIC SYNDROME IN GENERAL POPULATION WITHOUT CARDIOVASCULAR DISEASES. EVA STUDY

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Objective: To analyze the association of vitamin D with the metabolic syndrome (MS) and its components in general population without previous cardiovascular diseases.

Design and method: Cross-sectional study of general population without cardiovascular diseases. There were included 360 subjects between 35 and 75 years old (51% female), selected by random sampling stratified by age and gender groups using the Sanitary Card base of 4 urban health centers. The MS was defined following the recommendations of the National Cholesterol Education Program III. The circumference of the waist was measured with a tape measure, blood pressure with an OMRON tensiometer model M10-IT. Plasma glucose, lipid profile and 25 hydroxyvitamin D (25OH-D) were measured in blood.

Results: Mean values: age 56.8 ± 14.9 years (with MS = 65.4 ± 12.3 years, without MS = 55.5 ± 14.8 years, $p < 0.001$); 25OH-D17.90 ± 7.34ng/ml (with MS = 19.73 ± 8.03ng/ml, without MS 26.70 ± 13.34 ng/ml, $p < 0.001$), without gender differences ($p = 0.129$).

Prevalence of MS and its components: 14.3% (14.9% women, 13.7% men). Blood pressure increased 44.1% (40.0% women, 48.8% men), HDL-cholesterol under 13.4% (14.0% women, 12.7% men), triglycerides increased 14.2% (10.8% women, 18.1% men), abdominal obesity 41.9% (49.7% women, 32.7% men) and glycemia increased 14.6% (11.9% women, 17.9% men). They had values 25OH-D < 20ng/ml 33.6% (44.2% with MS, 31.8% without MS) ($p < 0.05$), 31% in women and 36% in men ($p > 0.05$). The presence of MS components had lower OH-D values, or $p < 0.05$ in HDL cholesterol, triglycerides and glycemia.
After adjusting by age and sex, we found positive correlation of 25OH-D with HDL-cholesterol ($r = 0.261$), negative with glycemia ($r = –0.165$), waist circumference ($r = –0.163$ and triglycerides ($r = –0.261$) No correlation with systolic and diastolic blood pressure.
In the logistic regression analysis after adjusting by age and sex, the subjects with MS had an OR = 1.690 (95% CI 0.913–3.130) of having figures of 25OH-D < 20 ng/ml ($p = 0.085$).

Conclusions: Subjects with MS have lower values of 25OH-D and correlates with HDL-cholesterol, triglycerides, glycemia and waist circumference. Subjects with MS have 1.7 times more risk of having 25 OH-D < 20 ng/ml.

ESTRADIOL AND LEPTIN OVEREXPRESSION HAVE INDEPENDENT MODES OF ACTION ON DECREASED FOOD INTAKE AND BODY WEIGHT IN MALES RATS

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Objective: We recently reported that male compared with female rats are less responsive to long-term central leptin overexpression, as assessed by decreased food intake and delta body weight. Moreover, males were more susceptible to development of leptin resistance than females suggesting that either male hormones mitigate or female hormones exacerbate leptin responses or both. To address the potential role of estradiol, we examined the treatment of leptin with or without estradiol on body weight parameters in male rats.

Design and method: To this end, we centrally delivered a viral vector to overexpress ether leptin or green fluorescence protein (GFP) into male rats that were simultaneously treated with either estradiol (25 mg/kg; S.C., daily) or vehicle in a two x two design. We examined chronic changes in food intake (FI), BW, and body composition over 26 days.

Results: BWs in both Leptin-vehicle and GFP-Estradiol were reduced compared with GFP-vehicle but more sustained in Leptin-Estradiol reminiscent of the pattern in females. Changes in FI were unique to each treatment, with a rapid decrease in Leptin-vehicle followed by gradual renormalization typical of leptin-induced leptin resistance. In contrast, the GFP-Estradiol decrease in FI was of lower amplitude ($P < 0.001$) but sustained over the 26 days ($P < 0.003$). The Leptin-Estradiol group was mostly additive but with a delay in leptin resistance typical of the pattern observed in female rats. Decreased body fat by TD-NMR was unique to each treatment paralleling FI. Phosphorylation of STAT3 (P-STAT3) was examined at death. No exogenous leptin was administered, thus detected P-STAT3 was due to central overexpressed leptin. P-STAT3 was greater in both leptin groups compared with GFP, but there was no difference between Leptin-vehicle and Leptin-Estradiol.

Conclusions: In conclusion, these data suggest that leptin and estradiol both decrease FI and BW, with the pattern of Leptin-Estradiol reminiscent of that observed in females. Furthermore, the estradiol-induced decrease in FI & BW does not involve P-STAT3. These data suggest that estradiol may be one factor in the increased leptin response and the mitigated leptin resistance observed in female rats.

INFLUENCE OF METABOLIC SYNDROME ON RENAL FUNCTION IN PATIENTS WITH HYPERTENSION

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Objective: Metabolic syndrome (MetS) is a condition linking insulin resistance, dyslipidemia, hyperglycemia, and hypertension that increases the risk of developing diabetes, cardiovascular disease, and subsequent cardiovascular morbidity and mortality. Hypertension is the key component of the metabolic syndrome. Aim of this study to estimate the impact of MetS on renal function in patients with hypertension.

Design and method: 312 hypertensive patients without history of chronic kidney disease (CKD) or cardiovascular disease at baseline were analyzed. Participants were categorized into two groups based on the presence of MetS at baseline. Group-1, 218 patients with MetS and Group-2, 94 hypertensives without MetS. Mean age of the patients was 52.4 ± 12.4 years, male-52%. Incident CKD was defined as eGFR < 90 ml/min per 1.73 m2 over 3 years. Metabolic syndrome was diagnosed according to the "Harmonized definition of the MetS".

Results: During the 3-year follow-up period, CKD developed in 27 subjects (12.5%) in the Group-1 and in 7 subjects (7.5%) in the Group-2. Compared to subjects without MetS, the odds ratio (OR; 95% confidence interval, CI) of incident CKD in those with MetS was 1.29 (1.09–1.52) after controlling for confounding factors. The risk of decline of eGFR was also higher in hypertensive patients with MetS than those without MetS (OR: 1.14, 95% CI: 1.02–1.27).

Conclusions: Metabolic syndrome is the risk factor for the development of CKD and patients with MetS should be treated more aggressive with reno-protective drugs.

EMPAGLIFLOZIN MAY ATTENUATE ADIPOSE TISSUE INFLAMMATION AND ARTERIAL STIFFNESS IN NORMOTENSIVE TYPE 2 DIABETICS

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Objective: Adipose tissue inflammation impairs arterial compliance at early stages of type 2 diabetes mellitus (T2DM). We aimed to assess the impact of empagliflozin as compared to sitagliptin on aortic stiffness and serum adiponectin (ADPN), an adipocytokine with insulin-sensitizing, anti-inflammatory and anti-atherogenic properties, in normotensive patients with T2DM.

Design and method: In this 24-week, randomized, open, parallel-group, controlled trial, 106 Caucasian normotensive T2DM subjects, inadequately controlled on metformin monotherapy (at least 1700 mg daily), were randomly assigned to receive 25 mg empagliflozin (n = 54) or 100 mg sitagliptin (n = 52) orally once daily. Arterial stiffness was assessed as carotid-femoral pulse wave velocity (PWV) measured via Complior (Artech Medical), whereas a sandwich enzyme-linked immunosorbent assay was employed for ADPN measurement. Office blood pressure (BP) was measured using a validated automated sphygmomanometer (Omron 705IT). Three measurements were taken at a 1-minute interval and were averaged for a single systolic/diastolic BP value.

Results: In the entire study population, mean age was 50.4 years, diabetes duration 6.1 years, baseline HbA1c 7.7%, fasting plasma glucose [FPG] 159 mg/dl, body mass index 30.2 ± 4.1 kg/m², systolic/diastolic BP 132.2/82.9 mmHg, glomerular filtration rate 89.9 mL/min/1.73m², PWV 13.0 ± 2.1 m/s and ADPN 6.0 ± 1.8 mg/ml at baseline. After 24 weeks significant changes were observed in HbA1c and FPG with both empagliflozin (–0.72% and –25.3 mg/dl, respectively) and sitagliptin (–0.70% and –23.2 mg/dl, respectively; $p < 0.001$ for all comparisons, between-group differences being non-significant), whereas hypoglycemia rates were comparable (2.1% with empagliflozin and 1.9% with sitagliptin; $p = 0.494$). BP values decreased with empagliflozin (–4.9 ± 0.9 mmHg [$p < 0.05$] systolic /–2.4 ± 0.4 mmHg [$p < 0.05$] diastolic), but not with sitagliptin (–1.3 ± 1.0 mmHg [$p = 0.672$] systolic /-0.1 ± 0.5 mmHg [$p = 0.848$] diastolic). Body weight declined by 3.8 kg ($p < 0.001$) with empagliflozin and 0.5 kg ($p = 0.082$) with sitagliptin ($p < 0.001$ for between-group difference). PWV decreased (-3.1 ± 0.3 m/s [$p < 0.001$] with empagliflozin and -1.6 ± 0.4 m/s [$p < 0.05$] with sitagliptin) and ADPN increased (3.3 ± 0.8 [$p < 0.001$] with empagliflozin and 1.3 ± 0.3 mg/L [$p < 0.05$] with sitagliptin), the differences being greater with empagliflozin ($p < 0.01$ for both comparisons).

Conclusions: Addition of empagliflozin to metformin may attenuate adipose tissue inflammation and arterial stiffness to a greater extent than sitagliptin in normotensive patients with T2DM.