Elevated first-trimester total bile acid is associated with the risk of subsequent gestational diabetes

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Aims/hypothesis Total bile acid (TBA) has been shown to be associated with the incidence of type 2 diabetes. Although TBA content correlates with insulin resistance, the relationship between TBA and gestational diabetes mellitus (GDM) is unclear. The aim of this study was to assess whether TBA level at first trimester pregnancy is associated with the occurrence of GDM.

Methods In this nested case–control study, biochemical parameters including serum TBA of 742 pregnant women were tested at 12 weeks of gestation and compared. Then 268 cases were diagnosed with GDM and 474 were diagnosed with normal glucose tolerance by 75 g oral glucose tolerance test (OGTT) performed at 24–28th weeks of gestation.

Results Serum TBA levels at early pregnant period were significantly higher in pregnant women with GDM compared with healthy pregnant women (2.3±1.4 μmol/L vs. 1.9±1.0 μmol/L, P < 0.001). The Spearman’s correlation analysis showed that TBA was positively associated with HOMA-IR and the occurrence of GDM (both P < 0.05). A binary logistic regression analysis after adjusting for other confounding variables revealed a significant and independent association between TBA and GDM [odds ratio (OR), 1.383; 95% confidence interval, 1.183-1.616, P < 0.001]. The pregnant women were divided into quartiles according to their serum TBA concentrations. Compared to the first quartile, the incidence and OR of GDM markedly increased in the fourth TBA quartile (both P < 0.05).

Conclusions/interpretation Serum TBA is closely linked with insulin resistance and GDM. Monitoring TBA at first trimester is helpful to identify women who are at risk for the subsequent development of GDM.
Pre-beta HDL in type 2 diabetes mellitus

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Introduction: Cellular cholesterol efflux is the first step of reverse cholesterol transport and the efficiency of this process is determined partly by the concentration of extracellular cholesterol acceptors like HDL. Pre-beta HDL mainly composes of apolipoprotein (apo) AI and phospholipids, and serves as the preferred acceptor of cellular cholesterol efflux mediated by the ATP-binding cassette transporter A1 (ABCA1). We have evaluated whether there are changes in pre-beta HDL concentration in type 2 diabetic patients independent of the levels of HDL cholesterol (HDL-C) and the effect on cholesterol efflux.

Methods: 500 type 2 diabetic patients and 360 non diabetic controls matched for age, gender and serum HDL-C levels were recruited. Subjects on lipid lowering agents were excluded. Plasma pre-beta HDL was measured by ELISA. In a random subgroup of subjects (115 diabetic patients and 70 control subjects), cholesterol efflux to serum mediated by ABCA1 was determined by measuring the transfer of [3H]cholesterol from Fu5AH cells expressing ABCA1 (induced by 22(R)-hydroxycholesterol and 9-cis-retinoic acid) to the medium containing the tested serum.

Results: There were no significant differences in the age and in the proportions of male/female subjects between the 2 groups. Despite the diabetic subjects having similar HDL-C levels (1.25 ± 0.35 mmol/L) and apo AI (1.32 ± 0.23 g/L) as controls (HDL-C: 1.25 ± 0.27 mmol/L, apo AI: 1.35 ± 0.22 g/L), serum pre-beta HDL was significantly lower in the diabetic patients [190.4 (123.0 - 260.5) ug/ml vs 201.6 (135.7–293.6) respectively, median (interquartile range), p<0.01]. Cholesterol efflux to serum mediated by ABCA1 was reduced in diabetic patients compared to control (1.40 ± 0.40% vs 1.72 ± 0.45 respectively, p<0.05). In the diabetic patients, cholesterol efflux mediated by ABCA1 correlated with log (pre-beta HDL) (r = 0.30, p<0.05) but not with HDL-C.

Conclusion: Low HDL-C level is common in patients with type 2 diabetes. However, even when type 2 diabetic patients were compared with a group of non-diabetic control subjects with similar HDL-C levels in our study, plasma pre-beta HDL level was significantly decreased in diabetic subjects and was associated with a reduction in cholesterol efflux to serum mediated by ABCA1 ex vivo. Our data therefore suggest that low pre-beta HDL level in type 2 diabetes might cause impairment in reverse cholesterol transport.
The association among Cardiotrophin-1, insulin resistance and nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. The disease is characterized by a wide spectrum of histological abnormalities ranging from simple hepatic steatosis, to nonalcoholic steatohepatitis, to liver fibrosis, and to cirrhosis. Although the precise mechanism of NAFLD remains incompletely understood, the most accepted pathophysiological model for NAFLD is the “two-hit hypothesis”.

Cardiotrophin-1 is one member of the interleukin-6 family cytokines. In the liver, previous studies demonstrated the hepatoprotective effects of cardiotrophin-1 in different models of acute liver injury. Moreover, cardiotrophin-1 was found to be upregulated in human and murine steatotic livers, and chronic administration of recombinant cardiotrophin-1 eliminated hepatic steatosis in obese mice. Recently, one animal study suggested that cardiotrophin-1 may be a promising therapy for insulin resistance and linked metabolic disorders. Although cardiotrophin-1 protects liver against acute injury, it is unclear whether cardiotrophin-1 is involved in the pathogenesis of NAFLD. Therefore, the aim of this study is to clarify the association between cardiotrophin-1 and NAFLD.

We recruited 287 subjects with (n=148) or without (n=139) NAFLD. All subjects received a health checkup and completed a structured questionnaire, and those who did not have a medical history of diabetes received a standard 75-g oral glucose tolerance test. Subjects with the following conditions or diseases were excluded: (1) alcohol consumption ≥ 20 g/day in the last year; (2) a positive test for hepatitis B surface antigen or hepatitis C antibody or other causes of liver disease; (3) serum creatinine > 1.5 mg/dl; (4) any acute or chronic inflammatory disease as determined by a leukocyte count > 10000/mm³ or clinical signs of infections; (5) any other major including generalized inflammation or advanced malignant disease.

Individuals with NAFLD had significant higher body mass index (BMI), systolic and diastolic blood pressure, fasting plasma glucose, homeostatic model assessment-insulin resistance (HOMA-IR) index, triglyceride, and high density lipoprotein (HDL) levels than those without it. Furthermore, subjects with NAFLD had significant higher cardiotrophin-1 concentrations than those without it. The results of multivariate linear regression analysis showed that NAFLD was positively associated with cardiotrophin-1 after adjusting for age, gender, BMI, HOMA-IR, systolic blood pressure (SBP), creatinine, triglyceride, HDL, hsCRP, smoking, and habitual exercise. Subjects with NAFLD had significant higher cardiotrophin-1 concentrations than those without it. Furthermore, NAFLD an independent predictor of cardiotrophin-1 levels after adjusting for age, gender, BMI, HOMA-IR, SBP, creatinine, triglyceride, HDL, hsCRP, smoking, and habitual exercise. Cardiotrophin-1 may be a surrogate biomarker of NAFLD.
Profiles of bile acids in subjects with different glucose tolerance after OGTT and their relationship with fibroblast growth factor 19

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Bile acids (BAs) can regulate glucose homeostasis and induce fibroblast growth factor 19 (FGF19) expressions through activating nuclear receptor farnesoid X receptor (FXR). Fasting serum FGF19 levels were markedly reduced in subjects with isolated-impaired fasting glucose (I-IFG) but not isolated-impaired glucose tolerance (I-IGT). However, the roles of BA compositions in glucose homeostasis and the possible relationship between serum BAs and FGF19 in humans remain unclear. Here, we investigated the dynamic change of serum BAs following oral glucose tolerance test (OGTT) among 71 subjects with 11 normal glucose tolerance (NGT), 10 I-IGT, 11 I-IFG, 12 combined glucose intolerance (CGI) and 27 type 2 diabetes mellitus (T2DM) subjects. Serum free BAs including chenodeoxycholic acid (CDCA), cholic acid, deoxycholic acid, and respective glycine conjugates were measured by liquid chromatography-mass spectrometry. Serum FGF19 levels were determined by ELISA. The association between BAs and FGF19 were also studied. The kinetics of glycine conjugates during OGTT showed a peak at 30min in all subjects, while free BA levels did not show significant elevation after glucose intake. Fasting serum CDCA levels in subjects with I-IFG, CGI and T2DM were significantly lower than those in NGT subjects (all p < 0.05), which was consistent with the trend of change in FGF19 levels in subjects with different glucose tolerance state. Fasting serum CDCA levels were found to be independently associated with fasting serum FGF19, and the significant association between FGF19 and plasma glucose no longer existed after adjustment for CDCA levels. Taken together, our results showed that fasting serum CDCA levels were decreased in subjects with increased fasting plasma glucose and positively correlated with FGF19, suggesting that the decrease of FGF19 in these subjects was at least partially due to their decrease of CDCA acting via FXR.
The role of irisin in components of metabolic syndrome, insulin secretion and resistance in schoolchildren

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Background: The prevalence of obesity worldwide has increased rapidly in recent decades, leading to increased morbidities and mortalities. Different from white adipose tissue, brown and beige adipose tissues contain abundant mitochondria, and help burn energy and create non-shivering thermogenesis. Enriching brown and beige adipose tissue may have potential as an anti-obesity strategy. Irisin, shaved from fibronectin type III domain containing 5 (FNDC5) in muscle tissue, increases after exercise and is believed to be the crucial factor in converting white adipose tissue to beige adipose tissue. In the present study, we explored the relationship between irisin levels and components of metabolic syndrome, fibrinolytic proteins, insulin secretion and resistance in schoolchildren in Taiwan.

Methods: There were 369 children (172 boys and 197 girls), aged 10.3 ± 1.5 years, enrolled from Taiwan elementary schools in our study. Irisin, anthropometry, metabolic syndrome components, insulin secretion, and resistance were measured. Subjects were divided into normal, overweight, and obese groups for evaluation of irisin in obesity. Finally, the relationship between irisin level and metabolic syndrome in boys and girls was analyzed.

Results: In boys, irisin levels were not associated with BMI percentile, body fat, blood pressure, lipid profiles, insulin secretion or resistance. The irisin levels in boys were associated, however, with age and fasting plasma glucose. After adjusting for age, the irisin level in boys was negatively related to fasting plasma glucose (r=-0.21, p=0.006) and weakly positively related to soluble plasma activator receptors (r=0.135, p=0.046). In girls, the irisin levels were associated with age and body fat. However, after adjusting of age, the irisin levels in girls were only positively related to fasting plasma glucose (r=1.49, p=0.038). In both genders, irisin levels were similar among normal, overweight, and obese groups, and between subjects with and without metabolic syndrome.

Conclusion: The irisin levels were not associated with metabolic syndrome and obesity in either boys or girls in Taiwan. However, we found that the irisin levels were negatively related to fasting plasma glucose in boys and positively related to fasting plasma glucose in girls. The contrary relationship between irisin and fasting plasma glucose in boys and girls needs further exploration in the future.
OL10-6

Association between 1,5-anhydroglucitol and early-phase insulin secretion in Chinese patients with newly diagnosed type 2 diabetes mellitus

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Objective: Glucose monitoring plays a key role in comprehensive management of diabetes. Insulin secretion deficiency and insulin resistance are involved in both the onset and progression of diabetes mellitus. The goal of this study was to probe into the relationships of glycated hemoglobin A1c (HbA1c) and 1,5-anhydroglucitol (1,5-AG) with insulin sensitivity and secretion in patients who were newly diagnosed with type 2 diabetes mellitus.

Methods: A total of 302 patients with newly diagnosed type 2 diabetes mellitus (166 men and 136 women; age range, 27 to 79 years old) were enrolled in this study. The homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of β cell function (HOMA-β) were calculated to evaluate the basal insulin sensitivity and secretory function, respectively. Insulinogenic index (IGI) was used for assessment of early-phase insulin secretion. HbA1c was detected by high-performance liquid chromatography. Serum 1,5-AG was assayed using the enzymatic method.

Results: When the subjects were stratified according to HbA1c quartiles, the trends analyses showed an upward trend for HOMA-IR and downward trends for both HOMA-β and IGI with increasing HbA1c quartiles (all P for trend < 0.001). Increased 1,5-AG quartiles were accompanied by a decreasing trend in HOMA-IR and increasing trends in HOMA-β and IGI (all P for trend < 0.001). Multiple stepwise regression analysis revealed that the independent correlations of HOMA-IR (standardized β = 0.525) and HOMA-β (standardized β = –0.673) with HbA1c were present (both P < 0.001) when HbA1c was defined as the dependent variable. Moreover, 1,5-AG was not only independently associated with HOMA-IR and HOMA-β (standardized β = –0.349 and 0.232, both P < 0.01), but also exhibited an independent and positive association with IGI (standardized β = 0.242, P < 0.001).

Conclusions: 1,5-AG level was not only correlated with basal insulin sensitivity and secretion, but also closely associated with early-phase insulin secretion in Chinese patients with newly diagnosed type 2 diabetes mellitus.
Increases in urinary N-acetyl-\(\beta\)-D-glucosaminidase excretion are associated with increased arterial thickness and presence of carotid plaques in type 2 diabetes

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N-acetyl-\(\beta\)-D-glucosaminidase (NAG) present in high concentration in lysosomes of proximal renal tubular cells is released into the urine after renal proximal tubule injury. Recently, urinary NAG has gained considerable attention because of its clinical implications as a sensitive and specific biomarker for early stage diabetic kidney disease. Several studies on associations between urinary NAG and micro-/macrovascular complications of diabetes have been reported. However, there is no data on association between urinary NAG and carotid intima media thickness (IMT) in patients with type 2 diabetes mellitus (T2D). The aim of this study was to investigate whether increases in urinary NAG are associated with arterial atherosclerosis assessed by carotid IMT. In this retrospective cross-sectional study, a total of 343 participants with T2D who had been tested for urinary NAG, carotid IMT, and gluco-metabolic parameters were enrolled. Demographic factors including age, sex, body mass index, smoking habit, blood pressure, duration of diabetes, and history of cardiovascular events were recorded. Mean age and duration of diabetes were 59.9 and 11.6 years, respectively. The participants with above median level of urinary NAG (11.4 (8.72-16.7) U/gCr) showed significantly higher values of mean and maximum carotid IMT (0.72 (0.60-0.84) vs 0.67 (0.58-0.77) mm and 0.90 (0.74-1.06) vs 0.82 (0.70-0.97) mm, respectively) than participants with median level of urinary NAG and below (4.89 (3.70-6.21) U/gCr). In participants with carotid plaques, the levels of urinary NAG were significantly higher than those without plaques (7.53 (5.24-12.0) vs 6.35 (4.40-8.35) U/gCr). In the multiple regression analysis, age (STD \(\beta=0.22\)), hypertension (STD \(\beta=0.13\)), and above median level (7.21 U/gCr) of urinary NAG (STD \(\beta=0.13\)) predicted higher values of maximum carotid IMT. Odds ratio for presence of carotid plaques after adjustment for age, hypertension, albuminuria, serum cholesterol, and estimated glomerular filtration rate was 1.86 (95% CI, 1.02-3.38) for increase in urinary NAG. In conclusion, urinary NAG was independently associated with carotid atherosclerosis in patients with T2D.
Validation of a novel biomarker panel, DNlite, for management of renal complication in type 1 diabetes

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Background:
In the previous studies, we have developed a novel biomarker panel, DNlite, for detecting kidney disease in patients with type 2 diabetic mellitus (T2DM) [Ref. 1, 2]. We also establish a novel scoring system, diabetic nephropathy score (DN_Score). DN_Score is a composite score built from fitting several urinary biomarkers, including alpha2-HS-glycoprotein precursor (AHSG), alpha-1-antitrypsin (A1AT) and acid-1-glycoprotein (AGP) in DNlite, to a statistical model that correlates highly with the stage of kidney disease in T2M. However, the development of diabetic nephropathy (DN) of T2DM is not as straightforward as it is in type 1 diabetic mellitus (T1DM) where there is a clear progression from normal renal function to hyperfiltration after about 5 years. In order to strengthen the application of DNlite, we conduct a large scale validation of DNlite in patients with T1DM.

Material and Methods:
447 patients with T1DM were enrolled and tested with DNlite. There were 206 male and 241 female participants. The mean age was 21.15±9.5 years. Related clinical parameters were well recorded. To access the severity and risk of kidney disease, patients were further categorized by GFR and albuminuria (KDIGO 2012 Clinical Practice Guideline).

Results:
The difference between patients with normo- and clinical albuminuria was very significant (p < 0.0001), and diagnostic accuracy using AUROC is up to 0.92. The DN_Score and stage in KDIGO is highly correlated. The difference of DN_Score between the low risk (1 if CKD) and the high risk (1 to 4+) is very significant (p < 0.0001). We also evaluated the correlation of DN_Score with metabolic variables. DN_Score was highly correlated with BMI, blood pressure, fasting plasma glucose, HbA1c and plasma triglyceride level.

Conclusion:
DN_Score is correlated significantly with the traditional indicators of DN in all stages of the disease in Type 1 DM. The application of DNlite in T1DM for detecting of DN has been demonstrated in this study. Furthermore, the application of DNlite for managing the DN prognosis in T1DM is under investigation.