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Introduction: Overweight and obesity often coexist with type 2 diabetes mellitus (DM2), worsening management and outcomes. Physical activity is an integral part of DM2 management. However, the interaction between fitness, body fat and mortality in diabetics has not been fully explored. Method: We assessed the association of exercise capacity and mortality risk in 3,601 individuals (mean age: 59±10) with DM2. All underwent exercise stress testing. Four fitness categories (quintiles) were established based on peak metabolic equivalents (METs) achieved: Least-Fit (<5.5 METs; n=945); Low-Fit: 5.6-7.0 METs; n=905); Moderate-Fit: 7.1-9 METs; n=868) and High-Fit (>9 METs; n=883). Individuals were also classified based on body mass index (BMI) as normal weight (BMI <25); overweight (BMI: 25-29.9) and obese (BMI ≥30). Results: There were 810 deaths (median follow-up 9.8 years). After controlling for age, risk factors and medications, we observed an inverse and graded association between exercise capacity and mortality risk for the entire cohort and within BMI categories, ranging from 33% to 70% (p<0.001). When comparing normal weight individuals with exercise capacity ≤7 METs, versus overweight/obese individuals with exercise capacity >7 METs, we noted that the risk for the overweight and obese, but fit individuals was 65% lower (p<0.001). Conclusion: An inverse and graded association between fitness and mortality risk in individuals with DM2 regardless of BMI. The risk for overweight and obese but fit individuals was approximately 65% lower when compared to those of normal weight and low-fit. This supports that fitness is a stronger predictor of mortality risk than ideal weight.

OPPORTUNITIES OF INSULIN PUMP THERAPY TO OVERCOME RESISTANCE TO EXOGENOUS-INJECTED INSULIN IN TYPE 2 DIABETES PATIENT- CLINICAL CASE

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Introduction: In some cases the increase of insulin doses in patients with type 2 diabetes does not reduce hyperglycemia. To overcome this condition is quite difficult. Clinical case: Women of 50 years old with type 2 diabetes (duration - 5 years) had inadequate glycemic control despite high insulin doses: Humulin NPH before: breakfast - 70 U, dinner - 60 U, supper - 60 U and Humalog – 48 U/day. Total 238 U/day (2.3 U/kg). Insulin was appointed a year ago, doses were gradually increased due to the high blood glucose levels. BMI - 34,1 kg/м2, HbA1c -7,7%. CGM showed changes from 5.5 to 15.0 mmol/l. Other endocrinology disorders were not detected. Patient had contraindications to metformin and pioglitazone. We used sensor augmented pump insulin therapy (Medtronic Paradigm Real-Time MMT-772). Basal rate (Humalog): from 24.00 to 8.00 - 3.5 U/h, from 8.00 to 24.00 – 4 U/h, bolus delivery - 10-16 U -3 times a day. After 4 days glycemic control was significantly improved and the daily dose of insulin decreased to 104 U/day (1.02 U/kg) with fasting glucose levels 6.1 - 7.0 mmol/l, postprandial 8-10 mmol/l. Conclusions: Inefficiency of large doses of insulin (resistance to exogenous-injected insulin) to a certain extent has been associated with chronic overdose of insulin. The use of insulin pump therapy allowed to overcome this condition and normalize glycemia in a type 2 diabetes patient.

SAFETY RESULTS FROM OCAPI: A EUROPEAN OBSERVATIONAL COHORT STUDY OF INSULIN GLULISINE-TREATED CHILDREN AGED 6 TO 12 YEARS WITH TYPE 1 DIABETES

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Aims: Children with type 1 diabetes mellitus (T1DM), especially younger children, are at risk of clinically significant hypoglycaemia. The aim of OCAPI was to evaluate the safety of insulin glulisine in children with T1DM in a clinical-practice setting. Methods: A 6-month, observational, prospective cohort study of children with T1DM aged 6–12y on a stable insulin regimen for ≥3 months, for whom insulin glulisine was prescribed. Primary endpoint was incidence of severe hypoglycaemia in children aged 6–12y. Secondary endpoints included incidence of severe hypoglycaemia (in children aged 6–8y), and symptomatic hypoglycaemia, injection-site/systemic hypersensitivity reactions, and medication error in both age groups. Results: 94 patients were analysed, of which 31 were aged 6–8y. The mean time from first prescription of insulin to inclusion was 2.3 and 2.8y in the 6–8 and 9–12y groups, respectively; mean HbA1c at study end was 8.2% and 8.3%, respectively. Basal insulin dose increased in both groups, whilst short-acting insulin dose increased in the 9–12y group only. Number of daily basal insulin injections did not change. Severe hypoglycaemia occurred in 3 patients (1 in 6–8y, 2 in 9–12y group), with an overall incidence of 6.6 events/100 patients/y. The incidence of symptomatic documented hypoglycaemia was higher in the 6–8y group compared with the 9–12y group (7007.2 vs 5717.5 events/100 patients/y). Conclusions: Although previous evidence suggests that hypoglycaemia is frequent in children with T1DM, these findings suggest insulin glulisine is a safe treatment option in this patient population.

MULTIMORBIDITY IN THE PATIENTS WITH DIABETES MELLITUS AND ARTERIAL HYPERTENSION AS BASIS FOR DIFFICULTIES IN DIAGNOSTICS AND TREATMENT

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Met treatment abrogates abnormal weight gain in many youth taking SGAs. However, no standard criteria exist regarding treatment initiation or dosing. To address these issues, two separate groups of residential psychiatric patients were started on Met: GROUP 1: those on SGAs for ≥ 2 months, with BMI was > 85th%ile and >7% body weight gain over the preceding 2 months or with BMI was > 95 %ile (n=36: age 13.8 ± 2.8 years [mean ± SD, 5.3-18y], 49% female, 45% African American); GROUP 2 (n=19) those started on Met and SGAs simultaneously. Met dose was increased over 2 months to weight stability. GROUP 1 weight increased 8.3% over 2 months prior to Met (BMIz from 1.35 ± 0.74 to 1.63 ± 0.58). Their BMIz stabilized over 4 months on Met (-0.01 ± 0.33), with continued efficacy after 6 months. Within GROUP 1, the BMIz change on Met was similar in those with or without a > 7% weight gain over 2 months prior to Met (0.04 ± 0.3 v -0.08 ± 0.35). GROUP 2 BMIz decreased more than GROUP 1 over 4 months on Met (from 2.24 ± 0.38 to 2.18 ± 0.37) and their daily Met dose was less (709.27 ± 258.87 mg v 829.15 ± 276.53 mg). In a controlled residential psychiatric setting, Met prevents weight gain on SGAs. This effect may be greater, requiring less Met, with simultaneous initiation of SGA and Met. Determining risk factors for SGA associated weight gain would allow more focused Met therapy.

GLYCOGEN SYNTHASE KINASE 3ß (GSK3ß) POSITIVELY REGULATES TLR3-MEDIATED CYTOKINES PRODUCTION

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Toll-like receptor 3 (TLR3) plays important roles in innate immune systems by producing type I interferons and proinflammatory cytokines. Although it is well known that GSK3ß is critical for the production of inflammatory cytokines in TLR-mediated signaling, how GSK3ß regulates TLR3 responses is poorly understood. To determine whether GSK3ß also regulates TLR3-mediated inflammatory cytokines production, we established the GSK3ß knockdown stable macrophage cell lines. Here we show that inhibition of GSK3ß attenuates the TLR3 agonist poly (I:C)-induced cytokines production. Suppression of GSK3ß expression drastically reduced the induction of c-fos protein by decreasing phosphorylation of extracellular signal-regulated kinase (ERK) and p38. In addition, GSK3ß interacts with TNF receptor associated factor 6 (TRAF6) and TGFß-activated kinase 1 (TAK1), which are required for TLR3-mediated mitogen-activated protein kinases (MAPKs) signaling cascade. Taken together, these findings demonstrate a regulatory function of GSK3β in TLR3-mediated proinflammatory cytokines production.

MOLECULAR SPECIES OF DIACYLGLYCEROL AND TRIGLYCERIDE, AND LIPOLYSIS IN ADIPOSE TISSUE OF OBESITY/DIABETES MODEL MICE

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A new genetic animal model of type 2 diabetes, the Tsumura Suzuki Obese Diabetes (TSOD) mouse, has been developed in 1999. The TSOD mouse develops a moderate degree of obesity and diabetes. The aim of this study was to investigate the levels of molecular species of triglycerides (TG) and diacylglycerol, and regulation of lipolysis in adipose tissue of TSOD mice. Methods: Twelve-week old TSOD and the age-matched control (TSNO) male mice were obtained. Epididymal adipose tissue was removed and extracted lipids by Bligh & Dyer"s method. Extracted lipids (tripalmitolein, trimyristin, triolein, tripalmitin, trilinolein, 1-palmitin-2-stearin-3-olein, 1-palmitin-2-olein-3-stearin, 1-myristin-2-olein-3-palmitin, 1-palmitin-2-linolein-3-stearin, 1-stearin-2-palmitin-3-olein, 1-palmitin-2-olein-3-linolein, 1,3-distearin, 1,3-dipalmitolein, 1,3-dipalmitin, 1,3-diolein, 1,3-dilinolein) were quantified by LC-MS (Orbitrap Discovery). The mRNA expressions of adipose tissue glycerol lipase (ATGL), hormone sensitive lipase (HSL), adipose phospholipase A2 (AdLPA2) and perilipin were also measured by real-time PCR. Results: There were no changes of the level of molecular species of TG between TSOD and TSNO except tripalmitin. Tripalmitin level in TSOD was significantly lower than that of TSNO. 1,3-Diolein level in TSOD were significantly higher than that in TSNO. 1,3-Dilinolein and 1,3-dipalmitin level in TSOD were also higher than those in TSNO, although those levels were not statistically significant. Expression of ATGL, HSL and perilipin was lower in TSOD than that in TSNO. Moreover, mRNA expression of AdPLA2 in TSOD was significantly higher than that in TSNO. Conclusions: Dysregulation of lipolysis and lipid metabolism in adipose tissue were observed in TSOD. These contribute in part to the development of obesity in TSOD mice.

GLYCAEMIC VARIABILITY AND HYPOGLYCAEMIC EPISODES WITH METFORMIN, GLARGINE, AND COMBINATION THERAPY IN T2DM USING CGM

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Aim: Antidiabetic treatments can lower HbA1c to target but may vary in their glycaemic variability (GV) and hypoglycaemia risk (HR) with insulin being discussed to show greatest GV and HR. We used continuous glucose monitoring (CGM) to assess GV and duration of hypoglycaemic episodes (HE) in early type 2 diabetes patients (T2DM) treated with monotherapy metformin (M) or glargine (GLA) compared to combination (GLA-M) therapy in longer duration T2DM. Methods: Pooled, retrospective, descriptive analysis of 185 eligible CGM profiles from T2DM patients with drug treatment over ≥6 months recorded in RCTs in our center (M=82; GLA=78; GLA-M=25). CGM (Medtronic) was performed for 72h to measure interstitial glucose (iG). AUC-24h, AUC-2h after standardized testmeal (TM), standard deviation of mean iG (SD-iG), mean average glucose excursions (MAGE), and day-to-day variation between day 2 and 3 of CGM were calculated. Threshold for HE was <3.0 mmol/l iG. Results: Characteristic of patients for M, GLA, and GLA-M were: age 64.0/64.0/64.7yrs; BMI: 30.0/29.7/30.4kg/m²; diabetes duration: 4.7/4.9/9.9yrs; HbA1c: 6.4/6.1/6.8%. CGM results: AUC-24h: 2005/1936/2087 (ns); AUC-2hTM: 217/204/231 (ns); SD-iG: 1.40/1.66/1.87mmol/l (p<0.05, M vs. GLA, GLA-M); MAGE: 3.7/4.3/5.4mmol/l (p<0.05, GLA-M vs. GLA, M). No difference in day-to-day variability was found between groups. Overall HE duration was similar in M, GLA and GLA-M groups (10.1/18.5/22.9 min/24h, ns). Conclusion: Early insulin treatment with glargine is not associated with a substantial increase in glycaemic variability and hypoglycaemia risk compared to metformin even when approaching tight HbA1c control in T2DM patients. Longer diabetes duration may increase glucose variability despite target glycaemic control.

EXERCISE CAPACITY AND MORTALITY IN OVERWEIGHT AND OBESE INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

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