

A novel mutation in the FOXP3 gene in a Palestinian infant affected with Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome

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Introduction: Neonatal Diabetes Mellitus (NDM) presents as uncontrolled hyperglycemia during the first 6 months of life. The majority presents with IUGR, FTT, decreased subcutaneous fat and low or undetectable C-peptide levels. NDM is classified into permanent (PNDM) and transient (TNDM). IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome results in approximately 4% of cases of males with PNDM. It is caused by mutations in the FOXP3 gene that codes for the scurfin protein which is a member of the forkhead/winged helix domain family of DNA-binding proteins. Here we describe a novel mutation in the FOXP3 gene in a Palestinian infant with IPEX syndrome.

Patients: A male infant was born at term to a healthy Palestinian parents with birth weight of 1700 gm. He presented shortly after birth with hyperglycemia, consistent with neonatal DM, persistent diarrhea, FTT and decreased subcutaneous fat. He died later with klebsiella sepsis. IPEX syndrome was suspected and confirmed by molecular testing.

Results: Molecular Data: DNA Sequencing of the FOXP3 gene in the deceased infant and his mother showed that he is hemizygous for a novel missense mutation (C424Y) in exon 12 of the gene, predicting substitution of tyrosine for cysteine at codon 424, while his mother is heterozygous for the same mutation.

Conclusions: This is the first report of IPEX syndrome in a family of Middle Eastern origin. FOXP3 gene sequencing should be performed in any male patient diagnosed with PNDM who develops other possible autoimmune associated conditions, even in the absence of the full IPEX syndrome.

Permanent Neonatal Diabetes Caused by Compound Heterozygous SUR1 Mutations with Opposite Functional Effects

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Introduction: Neonatal diabetes is a rare disorder, defined as diabetes mellitus occurring in the first 6 months of life. Heterozygous activating mutations in the KCNJ11 gene encoding the Kir6.2 subunit of the pancreatic beta cell KATP channel are the most common cause of permanent neonatal diabetes (PNDM). In addition, heterozygous activating mutations in the ABCC8 gene encoding the SUR1 regulatory subunit of this channel have recently been reported.

Patients: We describe a patient born after sperm donation. At the age of 3 months he presented with fever, convulsions and persistent hyperglycemia. HbA1C was 9.9%, anti-GAD antibodies were negative. Insulin treatment was started. Genetic analysis: Genomic DNA was extracted from peripheral lymphocytes, and direct sequence of the KCNJ11, ABCC8 and INS genes has been undertaken.

Results: Genetic analysis of the Kir6.2 and INS were normal. A compound heterozygote mutation for a novel missense mutation, S459R in exon 9, which is predicted to be an activating mutation, and a splicing mutation, c.3992-9G>A in intron 32, of the ABCC8 gene were found. The G>A mutation at nucleotide c.3992-9 (c.3992-9G>A) has previously been reported in patients with congenital hyperinsulinism and is an inactivating mutation. The S459R mutation is conserved across species and the mutations are on opposite parental chromosomes (in trans). The mother was found to be a carrier of the S459R mutation.

Conclusions: This is the first disease phenotype reported to be a result of compound heterozygosity for both gain- and loss-of-function mutations. Treatment with sulphonylurea was initiated and resulted in improved glycaemic control (HbA1C 6.5% compared with 9.4% during treatment with an insulin pump). We predict that the sperm donor is heterozygous for the c.3992-9G>A mutation and is therefore a carrier of congenital hyperinsulinism/neonatal diabetes. Appropriate genetic counseling was given.

CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH TYPE 1 DIABETES WHO DISCONTINUE INSULIN PUMP THERAPY: PREVALENCE AND CHARACTERISTICS

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Introduction: The Initiation and management of continuous subcutaneous insulin infusion (CSII) therapy in type 1 diabetes patients requires a multidisciplinary experienced team. This study was prompted by the high discontinuation rates for CSII quoted in the literature (25.7-49%). We aimed at characterizing patients discontinuing CSII therapy in our tertiary medical center and determine the dropout rate.

Methods: Medical charts of 459 type 1 diabetes patients (1.8-33 years, median 15) who initiated CSII therapy from 1998-2006 were reviewed. Fifty-nine patients discontinued CSII treatment (12.7%). Included in the study were 44 patients (9.5%), who discontinued CSII at least 3 months after initiation. The study group was compared to 93 randomly assigned CSII treated controls. Follow-up duration since CSII initiation was 4.3 ± 1.9 years.

Results: The dropout group had a significantly higher proportion of female patients than the control group (77% vs 57%, $p=0.024$). Comparable findings were noted for other background factors: rate of familial cases, confidentiality, ethnicity, age at diagnosis, pubertal stage and duration of diabetes at CSII initiation, height-SDS, weight-SDS, BMI-SDS, and rate of hypoglycemic and DKA episodes. There were no between-group differences in number of daily insulin injections and blood glucose measurements before CSII treatment. At CSII initiation, HbA1c was significantly higher in the dropout group than the controls ($8.57 \pm 1.29\%$ vs. $8.09 \pm 1.28\%$ $p=0.04$). This difference was maintained at the last follow-up.

Conclusions: The CSII dropout rate for children and young adults in our center is lower than reported. Female gender and poor metabolic control are associated with a higher risk of CSII dropout.

LONG TERM INSULIN PUMP TREATMENT IN GIRLS WITH TYPE 1 DIABETES AND EATING DISORDERS

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Introduction: The effect of long-term insulin pump therapy in adolescent females with type 1 diabetes (T1DM) and eating disorders (ED) was studied.

Patients: 63 girls age 10 years and above were included in the study. 48 were treated with pump (no-ED group), 15 had ED, of whom 8 were treated with pump (ED-pump-group), and 7 were treated with multiple daily injections (ED-MDI-group). Data were obtained from 24 months prior to pump insertion and up to 5 years subsequently.

Results: Girls in ED-pump-group had higher HbA1c compared to those in the no-ED group ($p=0.007$). There was no significant change in trend of HbA1c levels over time starting from 6 months prior to pump insertion in both the no-ED and the ED-pump groups ($p=0.86$ and 0.88 respectively). In the no-ED group, levels 0 to 6 months after pump insertion were significantly lower compared to baseline reference value taken within 6 months prior to pump insertion (7.67 vs. 8.03 % respectively $p=0.004$). Thereafter HbA1c levels were not different from baseline reference values. In the ED-group there was a slight but not significant decrease in HbA1c level prior to and after pump insertion. Girls with ED treated with pump had significantly lower HbA1c levels compared with to the ED-MDI-group 9.07 ± 1.33 vs. 10.40 ± 2.01 ($p=0.04$).

Conclusions: Treatment with pump was feasible in females with T1DM and ED and beneficial in lowering mean HbA1c levels for several months providing sustained metabolic control thereafter. Pump treatment was not associated with excess episodes of severe hypoglycemia or diabetic-keto-acidosis in these complex cases.

Baseline metabolic control, time to pump insertion, age and duration of pump treatment as factors affecting long-term metabolic control

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Introduction: To evaluate the independent effect of HbA1c levels at pump insertion on long-term metabolic control in children and adolescents with type 1 diabetes mellitus treated with pump.

Patients/ Methods: 113 children and adolescents with type 1 diabetes mellitus treated with insulin pump for up to 8 years. Linear trends and changes in HbA1c levels following pump insertion were performed by metabolic status prior to pump insertion, gender, age at pump insertion, duration between diagnosis of diabetes until pump insertion and duration on pump treatment.

Results: Patients with good metabolic control at baseline demonstrated increasing mean HbA1c levels with time (p for trend 0.002), despite this trend their mean HbA1c during follow-up period was significantly lower (7.3 ± 0.9) compared with higher baseline HbA1c levels groups. HbA1c levels of patients with poor baseline metabolic control decreased significantly immediately after pump insertion (9.4 ± 1.6 vs. 8.0 ± 1.2 , $p=0.0001$) and thereafter remained stable (p for trend=0.53). Shorter duration between diagnosis of diabetes and pump insertion was associated with better metabolic control. Poorer metabolic control was observed in patients 10-15 years old at pump insertion in comparison with patients <10 and >15 years. In multivariable analysis the metabolic status prior to pump insertion, time from diagnosis of diabetes to pump insertion and duration on pump were independently associated with long-term HbA1c levels.

Conclusions: Long-term response to pump treatment was dependent on baseline metabolic control. Early pump treatment had significant long-term impact on metabolic control.

Cellular mechanism of yeast derived oral insulin-mimetic material

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Introduction: The Glucose Tolerance Factor (GTF) is a dietary agent extracted from brewer's yeast. GTF reversed glucose intolerance in diabetic animals and humans. We found that oral treatment with GTF decreased blood glucose and lipids and potentiated insulin action in type 1 & 2 diabetic animals. GTF also decreased lipid peroxidation in blood and organs of the treated animals. We also found that addition of GTF to diabetic rats immediately with the induction of diabetes, inhibited the development of nephropathy and retinopathy in these animals. In vitro studies done in our laboratory on adipocytes and myocytes, showed that GTF increased glucose transport into the cells, in insulin-like mode. When a combination of GTF and insulin was supplemented to the cells, a synergy between GTF and insulin was detected. Binding of insulin to its receptor initiates a cascade of phosphorylations of several cellular proteins, regulating glucose transport, and lipid, glycogen and protein synthesis. The main objective of the present study was to investigate the effects of GTF on the cellular level and to study its involvement with insulin cascade.

Methods: GTF was extracted and partially purified from yeast according to a method developed in our laboratory. Differentiated 3T3-L1 cells were treated with either insulin or GTF. Cells were lysed, and western blot analysis was performed with anti-phospho tyrosine antibodies followed by stripping and reblotting with antibodies for total protein.

Results: Treatment of 3T3-L1 adipocytes with GTF increased general tyrosine phosphorylation of key proteins along insulin signaling pathway, in a time and dose-dependent manner. Whereas GTF did not affect tyrosine phosphorylation of insulin receptor (IR), it increased tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and stimulated the activation of Akt and p44/42 MAPK. Activation of Akt by GTF was inhibited by both wortmannin and LY294002, inhibitors directed against phosphatidylinositol-3-kinase (PI3K). The selective tyrosine kinase inhibitor HNMPA-(AM)3 blocked GTF-induced phosphorylation of tyrosine, Akt and MAPK, suggesting that GTF exerts its effects by activating upstream tyrosine kinases.

Conclusions: Our findings demonstrate that GTF acts through insulin-signaling pathway, and present GTF as a novel oral "insulin-like" material, for future treatment of diabetes.

Glucose homeostasis after total pancreatectomy- A report of two cases from a single center and review of the literature

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Introduction: Total pancreatectomy (TP) causes severe deficiency of both exocrine and endocrine pancreatic function. However, patients with diabetes due to TP have metabolic features that are different from Type 1 diabetes mellitus (DMT1). The aim of this analysis was to evaluate daily glucose profile, insulin requirements and treatment protocols in two patients who underwent TP in our institution.

Patients/ Methods: Review of the literature according to keywords: total pancreatectomy, glucose, diabetes mellitus. Review of patient's records of self monitored blood glucose at fasting, pre-prandial, post-prandial state and at midnight three to four weeks post operation.

Results: Eight articles were found using aforementioned criteria. Several important issues emerge: insulin requirement is lower in patients after TP than in patients with DMT1, patients are glucagon deficient with no increase after hypoglycemia or arginine infusion, the area under the curve of epineprine and norepinephrine elevation in response to hypoglycemia is the same as in DMT1 but the timing of elevation appears later, and finally, gluconeogenic precursors are higher in patients with TP due to lack of glucagon, which make them highly prone to severe hypoglycemia. Patient A, a 50 years old female, was operated for non-functioning pancreatic neuroendocrine tumor. Body mass index (BMI) 17kg/m². Average daily insulin dosage 18 units (0.33units/kg). Patient B, 35 years old male with clinical MEN1 syndrome on chronic hydrocortisone replacement, operated for multiple non-functioning pancreatic neuroendocrine lesions, BMI 23kg/m², treated with 30-32 units of insulin per day (0.43-0.46units/kg). Treatment protocol is the same for both patients with insulin glargine at 6 AM and insulin aspart before meals (one unit insulin per 15 grams carbohydrates and late carbohydrate snack at bedtime without insulin). Both patients maintain near normal daily glucose profile without major hypoglycemic episodes.

Conclusions: Our two patients show high insulin sensitivity. This observation matches the scarce data from former literature. The treatment protocol achieves near normal glucose control with minor variability. Adding carbohydrate at bedtime reduces early morning hypoglycemia.

Prevalence of Anemia in Diabetic Patients with Normal Serum Creatinine

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Introduction: Anemia is more prevalent in diabetic patients than in the general population. Renal impairment, medications and inflammation of chronic disease are possible contributory factors. Most studies evaluating the prevalence and etiology of anemia in diabetic patients have focused on diabetic patients in tertiary – care settings, often with renal failure, a known cause of anemia. We decided to determine the prevalence of anemia, in a cohort of patients with diabetes and normal creatinine in a primary care clinic.

Patients: Retrospective cohort study comparing anemic and non-anemic adult diabetic patients. Diabetic patients over 18 years-old were identified using the computerized database of a primary care clinic. Patients with hemoglobin ≤ 13.7 g/dl (males < 60 y), ≤ 13.2 g/dl (males > 60 y) or ≤ 12.2 g/dl (females) with no known cause of anemia were identified and compared to non-anemic diabetic patients. All patients had normal creatinine levels (males < 1.5 mg/dl, females < 1.4 mg/dl).

Results: 594 eligible diabetic patients with normal creatinine levels were identified. One hundred and ninety two patients (32%) had anemia. Advanced age, higher levels of urea, creatinine, reduced glomerular filtration rate, and reduced iron were more common in anemic diabetics (table 1). Glitazone, insulin, and angiotensin receptor blocker therapy were more prevalent in anemic patients. There was no difference in sex, glycosylated hemoglobin (HbA1c) or serum ferritin between the anemic and non-anemic patients

Conclusions: The prevalence of anemia in unselected diabetics with normal creatinine levels, in a community clinic was 32%. Factors associated with anemia were older age, relatively reduced renal function, decreased serum iron and the use of glitazones, insulin and ARB. Glycemic control did not differ between anemic and non-anemic patients. Future studies should evaluate whether reversal of anemia in diabetics improves cardiovascular and renal function, and reduces mortality.

Angiotensin 1-7 As A Potential Novel Therapy for the Metabolic Syndrome: Initial Proof of Concept in the Fructose- Fed Rat.

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Introduction: Angiotensin 1-7 (Ang 1-7) has multiple beneficial effects in the cardiovascular system, which are exerted through the Mas receptor and linked to attenuation of deleterious effects of angiotensin II (Ang II). Since Mas is expressed in fat tissue and Mas knockout leads to the metabolic syndrome (MetSyn) in mice, we reasoned that Ang 1-7 may serve as a potential drug for the MetSyn.

Methods: We used a model of the acquired MetSyn in rats fed high-fructose/low magnesium diet over 13 wks. Animals on a normal (control, n=15) or fructose diet (n=15) were further divided into a vehicle- or Ang 1-7 (576 µg/kg/day, s.c., via an Aldzet pump, 1 month) treatment. A cross-over design was implemented, such that after one month, the Ang1-7 arm was switched to receive vehicle and vice versa.

Results: First, Mas mRNA expressed in rat fat tissue showed 94% homology with the musculus MAS1 mRNA (NM_008552.3). Among the various fat depots, the lowest Mas mRNA expression was seen in mesenteric and retroperitoneal fat (p<0.05). Second, the increased serum triglycerides typical for this model were lowered by 4 weeks of Ang 1-7 (from 306.2±24.8 to 203.2±28mg/dl, p=0.029). Third, Ang 1-7 treatment did not affect body weight but significantly attenuated the hyperinsulinemia elicited by the fructose diet (fasting insulin 20±3. vs 27.3±1.41 µU/ml, p=0.02). In response to intraperitoneal glucose challenge (2gram/kg), Ang 1-7- treated, fructose fed rats showed diminished rise in serum glucose (P<0.05). Further evidence that Ang 1-7 improves insulin sensitivity was obtained by intraperitoneal insulin tolerance test (0.8U insulin/kg), which resulted in larger reduction in serum glucose levels in the Ang1-7 treated, fructose-fed rats (44.8±2.6mg/dl vs 58.8±3.16mg/dl at 15 minutes past injection, p<0.03). Fourth, in cultured murine 3T3 pre-adipocytes and adipocytes, Ang II induced a twofold increase in oxidative stress as assessed by the NBT method, which was nearly entirely inhibited by Ang 1-7 (p<0.05).

Conclusions: Ang 1-7 significantly minimized several metabolic derangements in the high fructose rat, including fasting hyperinsulinemia, insulin resistance and hypertriglyceridemia. These beneficial effects were independent of body weight and could be related, in part, to the anti-oxidative influence of Ang1-7 in adipose tissue.

Obesity in survivors of childhood malignancies

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Introduction: Increased incidence of obesity is observed in survivors of childhood cancer. In a previous analysis we found that the rates of obesity in survivors of childhood malignancy were twice as high as the reported rates in Israeli children. Obese patients were significantly younger than normal-weight patients. The aim of the current study was to evaluate the trends in incidence of obesity in our patients after 3.3 ± 1.4 additional years of follow-up, in order to better understand the higher rates of obesity in younger patients.

Patients: 149 patients (51% males) were prospectively evaluated in our late effects clinic for 7.4 ± 3.9 years after diagnosis. The mean age at last evaluation was 14.5 ± 9.1 years. 25.2% of our patients were treated for leukemia, 12.9% were treated for lymphoma, 24.5% had brain tumors, 16.3% had solid tumors, and 12.2% had non-malignant hematologic diseases.

Results: At last measurement, 27.2% of the patients were overweight (BMI>85th percentile for age), while 13.6% were obese (BMI>95th percentile), similar to our previous findings. The prevalence of obesity was highest in patients with brain tumors (38.9%), leukemia (35.1%), and optic glioma (37.5%). Overweight patients were significantly ($p=0.049$) younger compared to normal weight patients. BMI-SDS of patients with brain tumors increased significantly ($p=0.043$) with time, while BMI-SDS of other patients' groups did not change. BMI-SDS of patients who were overweight at the initial evaluation did not change with time.

Conclusions: Obesity is a common sequel of childhood malignancy, and is associated mainly with leukemia and with brain tumors. The higher prevalence of obesity in younger patients is probably attributable to the higher frequency of these diseases in them. Overweight patients remained overweight as time went by. These findings enable targeting of at-risk patients in order to prevent long-term complications including the metabolic syndrome and cardiovascular diseases.

Adiponectin and vascular properties in obese patients: Is it a novel biomarker of early atherosclerosis?

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Introduction: Adiponectin is an adipocyte-derived collagen-like protein, highly specific to adipose tissue and may represent an important link between obesity and atherosclerosis. The present study was designed to investigate a possible association between serum adiponectin levels and early vascular changes in obese patients as determined by intima media thickness (IMT) and arterial pulse-wave contour analysis.

Patients: Obese subjects (n=47) were evaluated for arterial structure and function, metabolic parameters and serum adiponectin levels. IMT was measured by ultrasound. Arterial elasticity was evaluated using pulse wave contour analysis. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR).

Results: Adiponectin was significantly, inversely associated with mean IMT ($r=-0.369$, $p=0.011$) and significantly positively associated with large artery elasticity index (LAEI) ($r=0.467$, $p=0.001$) as well as small artery elasticity index (SAEI) ($r=0.462$, $p=0.001$). In separate multivariate models, adiponectin remained significantly associated with mean IMT, LAEI, SAEI even after adjustment for cardiovascular confounders. Among metabolic parameters, adiponectin was significantly, positively associated with HDL cholesterol and inversely associated with triglycerides. Adiponectin was significantly, inversely associated with fasting insulin and HOMA-IR. Additionally, a marginally inverse association between adiponectin and ALT was observed.

Conclusions: In the present study, serum adiponectin levels were significantly associated with indices of subclinical atherosclerosis such as IMT and arterial compliance in obese patients. This association was independent of traditional cardiovascular risk factors.

The Involvement of S-nitrosylation in Adipose Tissue Dysfunction

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Introduction: S-nitrosylation of protein cysteinyl residues has been suggested to be an important nitric oxide-dependent post-translational modification. Oxidative and Nitrosative stress occurs systemically in diabetes, and was suggested to be involved in the development of muscle insulin resistance in various experimental systems. While increased oxidative stress is established in fat tissue, it is unknown whether increased nitrosative stress occurs in fat tissue in obesity, and if so, what is its role in the induction of adipose tissue dysfunction. Aims: i) To evaluate whether protein S-nitrosylation occurs in adipose tissue of nutritional (high-fat-diet) and genetic (ob/ob) models of obesity, and in human obesity. ii) To assess in 3T3-L1 adipocytes the ability of NO donors (GSNO, SNAP) to induce adipose dysfunction

Methods: For studying in-vivo protein S-nitrosylation in obesity we utilized two animal models (male C57BL/6J mice after 20 weeks of high fat feeding, and ob/ob mice at the age of 16 weeks), and human omental fat biopsies. S-nitrosylation was evaluated in fat tissue by the Biotin switch technique. For studying the effect of S-nitrosylation in 3T3-L1 adipocytes the cells were exposed to 1mM GSNO/0.5mM SNAP for 24h.

Results: 1. Total S-nitrosylation of adipose tissue proteins obtained for HFD and ob/ob mice was elevated compared to lean mice. In accordance, human omental fat tissues obtained from obese women demonstrate increased S-nitrosylation. In addition, in HFD fat tissue we obtained enhanced iNOS and decreased Thioredoxin reductase expression which may underlie increased S-nitrosylation. 2. The NO donors increase S-nitrosylation in 3T3-L1 adipocytes and decrease adiponectin expression and secretion in 3T3-L1 adipocytes. 3. The NO donors reduce insulin-stimulated PKB but not GSK3 phosphorylation in 3T3-L1 adipocytes and there was no effect on insulin-stimulated glucose uptake. 4. The NO donors inhibit insulin-induced anti-lipolysis in 3T3-L1 adipocytes.

Conclusions: Obesity is associated with increased protein S-nitrosylation in adipose tissue, which is associated with enhanced iNOS and decreased thioredoxin reductase expression as potential underlying mechanisms. The prevention of insulin-induced anti-lipolysis and the decrease in adiponectin expression and secretion caused by NO donors protein in adipocytes in culture may underscore the potential of protein S-nitrosylation to induce adipocyte dysfunction in obesity.

Characterization of the cellular and molecular effects of insulin glargine in colon cancer cells

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Introduction: Diabetes mellitus is a heterogeneous group of diseases characterized by high blood glucose due to impaired insulin secretion or action. Insulin analogues have been developed in recent years by modifying the insulin molecule in order to achieve better pharmacokinetic properties able to mimic the endogenous secreted insulin. Glargine (Lantus® Sanofi Aventis), a long-acting analogue, harbors minor changes in a molecular domain that do not affect insulin receptor (IR) affinity. However, this domain appears to be important for IGF-I receptor (IGF-IR) affinity. Previous research in our laboratory has shown that glargine induced proliferation of colon and other cancer cell lines in a dose- and time-dependent manner and also exhibited an anti-apoptotic effect. Our working hypothesis is that long-acting insulin analogues display enhanced affinity towards the IGF-IR and, therefore, exhibit IGF-I-like activities, including stimulation of cellular proliferation. In this study we examined the molecular basis of the mitogenic and anti-apoptotic effects of the long-acting insulin analogue glargine in comparison to regular insulin and IGF-I in colon cancer cells.

Patients/ Methods: IR and IGF-IR activation were evaluated using immunoprecipitation assays. The potential antiapoptotic activities of the analogue were evaluated using an Annexin V/FITC kit. The effects on cell cycle progression were tested by FACS analysis. Visualization of the glargine-induced IGF-IR internalization was done by transfection of a GFP-containing IGF-IR-encoding plasmid followed by imaging using confocal microscopy.

Results: Results obtained showed that glargine was able to phosphorylate both the IR and IGF-IR. Activation of IGF-IR by glargine resembled its activation by IGF-I in terms of doses and time frame. Dose-dependent experiments revealed that glargine activated the IGF-IR at 5-fold lower concentrations than those required to activate the IR. In addition, glargine induced a sustained IR phosphorylation (up to 6 hours) whereas it activated the IGF-IR in a biphasic fashion. Finally, biological studies revealed that glargine exhibited an IGF-I-like anti-apoptotic effect and enhanced the proportion of cells in S-phase.

Conclusions: Our data is consistent with the notion that glargine exhibits IGF-I-like mitogenic and antiapoptotic activities in cancer cells through its ability to interact with the IGF-IR. The different binding characteristics of glargine to the IGF-IR, in comparison to regular insulin, seem to promote abnormal signaling and, eventually, lead to different biological actions. The clinical implication of these findings remain to be established.