Correlation of endocrine and exocrine pancreatic functions in diabetes mellitus type 2 patients: the effect of GLP-1 receptor agonist and DPP-4 inhibitor treatment

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SUMMARY

Background: A strong positive correlation between pancreatic endocrine and exocrine function has previously been described in chronic pancreatitis. Here, we examined this correlation in diabetes mellitus type 2 patients treated with recently introduced incretin-based therapies including the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor linagliptin.

Methods: The study group included 39 subjects with type 2 diabetes mellitus treated with metformin and randomized to 3 months of treatment with exenatide, linagliptin or the sulphonylurea derivate gliclazid MR as active comparator. Laboratory markers of endocrine (fasting blood glucose, C-peptide, HbA_{1c}) and exocrine function (faecal elastase-1 - FELA and ^{13}C-mixed triglyceride breath test - ^{13}C-MTG) were evaluated before and after 3 months of therapy. The results were statistically analysed by t-tests and paired correlations (and by one-sample Wilcoxon tests or Spearman rank correlations, alternatively) using SPSS software.

Results: In the whole group a significant correlation of ^{13}C-MTG test with C-peptide (Spearman's r=-0.323; p=0.048) and HbA_{1c} (r=-0.397; p=0.008) was found, while no correlation could be seen for FELA. HbA_{1c} was significantly reduced by all three types of therapy (p=0.019; p=0.025 and p=0.003 for exenatide, linagliptin and gliclazid MR, respectively), whereas no parameter of pancreatic exocrine function was changed by any of the antidiabetic drugs. After treatment, the only endocrine-exocrine correlation to remain preserved was the association between HbA_{1c} and ^{13}C-MTG test (p=0,014) in the linagliptin group.

Conclusions: A correlation between endocrine and exocrine pancreatic function as measured by HbA_{1c}, C-peptide and ^{13}C-MTG test was detected in type 2 diabetic subjects on metformin monotherapy. This endocrine-exocrine correlation was preserved only by DPP-4 inhibitor treatment.
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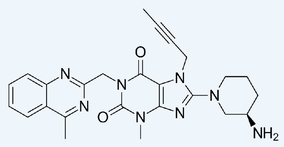
INCRETIN-BASED THERAPIES

Incretins are peptide hormones released from the small intestine upon meal ingestion that stimulate insulin secretion from pancreatic β-cells and reduce excessive glucagon secretion from pancreatic α-cells in a glucose-dependent manner resulting in lowering of blood glucose. Their biological half-life is extremely short (1.5-5 min) due to their rapid degradation by the enzyme **DPP-4** (dipeptydilpeptidase 4). Therapies based on the main incretin, **GLP-1** (glucagon-like peptide 1), include **GLP-1 receptor mimetics** that are resistant to DPP-4 degradation and **DPP-4 inhibitors** that inhibit DPP-4, resulting in improved glucose control with minimal risk of hypoglycemia. Except of glucose lowering, other effects were also suggested for both drug classes based on experimental and early clinical data, among them β-cell protection and proliferation.

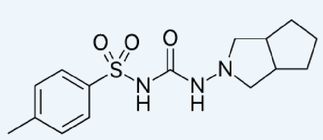
Gliclazide



Exenatide

H–His–Gly–Glu–Gly–Thr–Phe–Thr–
–Ser–Asp–Leu–Ser–Lys–Gln–Met–
–Glu–Glu–Glu–Ala–Val–Arg–Leu–
–Phe–Ile–Glu–Trp–Leu–Lys–Asn–
–Gly–Gly–Pro–Ser–Ser–Gly–Ala–
–Pro–Pro–Pro–Ser–NH_2

Linagliptin



EXOCRINE/ENDOCRINE PANCREATIC TESTS

^{13}C-MIXED TRIGLYCERIDE BREATH TEST

Modified procedure:
Stimulation meal - 4 crisp slices, maize with fibres (without cholesterol, gluten-free), 2 x 10g Rama (vegetable fat without milk proteins), test substance - 250mg ^{13}C-MTG **stirred into vegetable fat, hourly breath-bag sampling (1-6 hr)**
Breath test analytics:
HeliFAN plus 4 channel system, FAN (Germany) with NDIRS opto-acustic detector unit, six hours cummulative recovery of of $^{13}CO_2$: $^{12}CO_2$ calculated with BMR CO_2 production calculated by weight, height, sex and age
normal cut-off level: 30 %

FECAL ELASTASE ELISA TEST

Schebo Biotech (Germany) with monoclonal antibody to elastase IIa isotype normal cut-off level: 200 μg/g

HbA_{1c} AND C-PEPTIDE TESTS

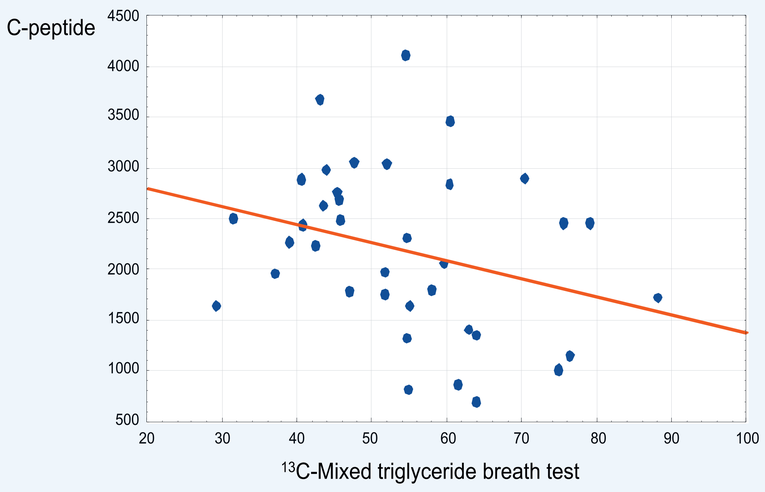
Blood samples were collected in vacuum tubes with gel, centrifuged and serum was separated for C-peptide assay, full blood was collected with EDTA vacuum tubes for HbA_{1c} assay.
The test C-peptide was done within 4 hours of the collection of samples using the electro-chemiluminescence immunoassay (ECLIA) on Roche Modular module immunoassay analyser.
The test for plasma HbA_{1c} was done by ionexchange high-performance liquid chromatography (HPLC) on BioRad Variant II TURBO analyser.

Exenatide is a **39-amino-acid peptide,** an insulin secretagogue, with glucoregulatory effects. It binds to the intact human **Glucagon-like peptide-1 receptor** (GLP-1R) in a similar way as the human peptideglucagon-like peptide-1 (GLP-1), both displaying similar biological properties and regulating glucose metabolism and insulin secretion. Exenatide enhances glucose-dependent insulin secretion by the pancreatic β-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying, most probably through peripehral and central activation of the vagal nerve. The half life of exenatide is 2.4 hours requiring it to be administered twice daily and its circulating concentrations are approx. 3-5 higher than endogenous GLP-1 levels.

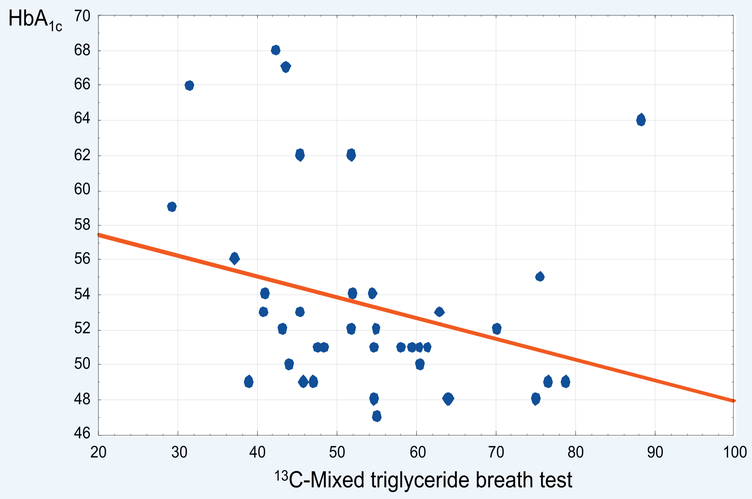
Linagliptin, chemically a **purin and quinalzoline derivate,** is a member of the DPP-4 inhibitor class of antidiabetic drugs that exerts its glucose-lowering actions by prolonging the biological half-life of endogenous GLP-1, as it **blocks its degradation by DPP-4**. The resulting glucose-lowering actions of linagliptin are similar to exenatide, albeit without its gastric motility-reducing effects. Linagliptin binds to DPP-4 in a reversible manner with a half life of >100 hours and elevates the levels of GLP-1 to high-normal physiological range. At therapeutic levels the binding of linagliptin is selective to DPP-4 and does not affect other DPP isoforms (e.g. DPP-8 or -9).

Gliclazide, a **sufonylurea derivate**, selectively **binds to sulfonylurea receptors (SUR-1)** on the surface of the pancreatic β-cells. This binding effectively closes the K+ ion channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca++ ion channels to open increasing the Ca++ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocytosis of insulin vesicles leading to insulin release. Gliclazide undergoes extensive metabolism to several inactive metabolites in human beings, mainly methylhydroxygliclazide and carboxygliclazide. CYP2C9 is involved in the formation of hydroxygliclazide in human liver microsomes and the pharmacokinetics of gliclazide MR are affected mainly by CYP2C19 genetic polymorphism instead of CYP2C9 genetic polymorphism.

Scatterplot of C-peptide values to ^{13}C-Mixed triglyceride breath test values in group of 39 subjects with type 2 diabetes mellitus before incretin-based therapy, R square (linear fit)
r = -0.297, regression value r^2 = 0.088, with **correlation significance p = 0.074**



Scatterplot of HbA_{1c} values to ^{13}C-Mixed triglyceride breath test values in group of 39 subjects with type 2 diabetes mellitus before incretin-based therapy, R square (linear fit)
r = -0.284, regression value r^2 = 0.081, with **correlation significance p = 0.083**



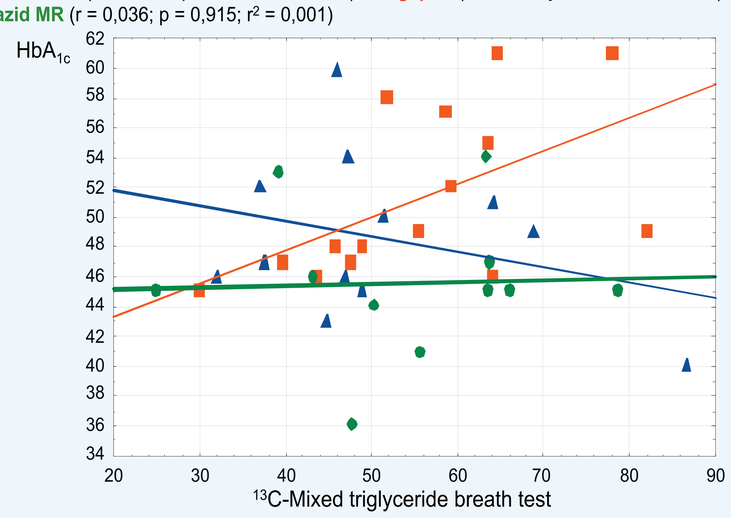
EXOCRINE/ENDOCRINE PANCREATIC TESTS

DM2 therapy	FELA	MTG	HbA_{1c}	C-peptide
before therapy	1096	52.5	54.63	2216
Exenatide	764	51.7	48.63	2145
significance (paired t-test)	0,840	0,811	**0,097**	0,948

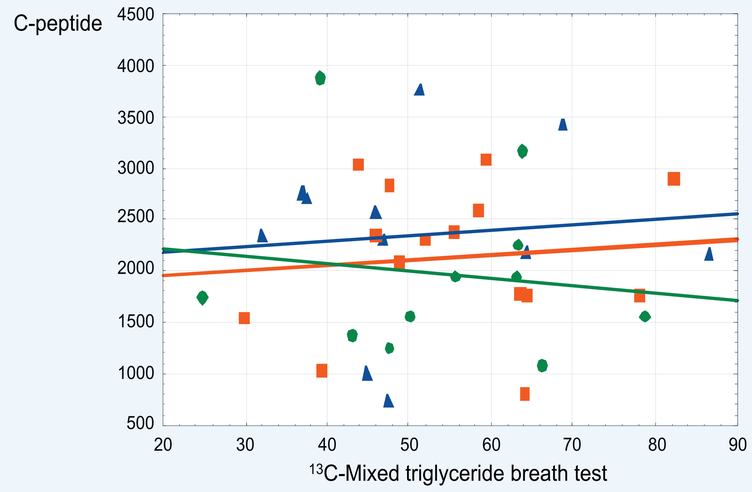
DM2 therapy	FELA	MTG	HbA_{1c}	C-peptide
before therapy	1410	57.39	52.66	2022
Linagliptin	1377	56.53	47.93	2070
significance (paired t-test)	0,896	0,722	**0,087**	0,861

DM2 therapy	FELA	MTG	HbA_{1c}	C-peptide
before therapy	800	49.59	53.88	2311
Gliclazid MR	602	49.16	50.87	2147
significance (paired t-test)	**0,407**	0,632	**0,002**	0,844

Scatterplots of HbA_{1c} values to ^{13}C-Mixed triglyceride breath test values
(R square - linear fit, regression value r^2 and correlation significance p) in groups treated with **exenatide** (r = -0,297; p = 0,348; r^2 = 0,088), **linagliptin** (r = 0,549; **p = 0,033**; r^2 = 0,302) **gliclazid MR** (r = 0,036; p = 0,915; r^2 = 0,001)



Scatterplots of C-peptide values to ^{13}C-Mixed triglyceride breath test values
(R square - linear fit, regression value r^2 and correlation significance p) in groups treated with **exenatide** (r = 0,097; p = 0,776; r^2 = 0,009), **linagliptin** (r = 0,098; p = 0,725; r^2 = 0,009) **gliclazid MR** (r = -0,127; p = 0,709; r^2 = 0,016)



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