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Liraglutide exerts an anti-inflammatory action in obese patients with type 2 diabetes

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Introduction. Liraglutide (L) is the analogue of human glucagon-like peptide 1 which stimulates glucose-dependent insulin secretion and can modify the level of inflammatory biomarkers.

L can influence NF-kB inflammatory cascade, but the mechanisms of anti-inflammatory activities of L remain to be determined. In animal models L influenced an activity of Sirtuin 1(SIRT1). Moreover, recent evidences strongly suggest that SIRT1 up-regulation may serve as a potent therapeutic approach against development and progression of diabetic complications. The aim of this study was to investigate L effects directed on the pro-inflammatory NF-kB pathway and expression of SIRT1 in obese patients with type 2 diabetes mellitus (DM).

Materials and Methods. 15 obese patients with type 2 diabetes were studied, all using metformin (1-2 g/day) and sulfonylurea (glimiperide). All patients received L 1.2 mg daily add-on to stable therapy for 6 weeks. Blood samples were collected before, 6 weeks after start of treatment and after an overnight fast 6 weeks after stopping L, mononuclear cells (MNC) were isolated. The mRNA expressions of TNF-α, TLR2, TLR4, NOD1, IL-2 and SIRT1 were measured in MNC by RT-PCR. Ceruloplasmin concentration was measured in plasma by photometric method.

Results. In this add-on pilot clinical investigation we received new data that L can inhibit proinflammatory NF-kB pathway by increased *SIRT1* expression in obese patients with type 2 DM improving metabolic profile. The mRNA expression in MNC of TNF-α, IkB, TLR2, TLR4, and plasma ceruloplasmin fell after 6 weeks of L. Expressions of IL-2 and NOD-1 were stable. There was a significant increase of SIRT1 mRNA expression. The mRNA expression in MNC of TNF-α, IkB, TLR2, TLR4, NOD1, SIRT1 and ceruloplasmin concentrations did not reverse to baseline levels after 6 weeks stopping of L treatment. IL-2 expression decreased in comparison with basic level.

Conclusions. L has a potent anti-inflammatory effect as do GLP-1 agonists due to inhibition of NF-kB pathways and up-regulate SIRT1 expression, down-regulating pro-inflammatory factors including cytokines (TNF-α), extra- and intracellular receptors (TLR2, TLR4), and inflammation markers such as ceruloplasmin. Long lasting effects of L can be mediated by epigenetic regulation of NF-kB pathway by SIRT-1.

Key words: glucagon-like peptide 1 (GLP-1), liraglutide; diabetes; obesity; NF-kB; SIRT1, mediators of inflammation.

INTRODUCTION

Liraglutide (L) is the analogue of human glucagon-like peptide 1 which stimulates glucose-dependent insulin secretion and can modify cardio-vascular risk biomarkers such as hs-CRP, IL- 6, and TNF-α [1]. Another analogue of GLP-1 exenatide has a potent and rapid anti-inflammatory effect with a significant reduction in reactive oxygen species generation and the mRNA expression of several inflammatory mediators (TNF-α, JNK-1, TLR-2, TLR-4, IL-1, SOCS-3) in mononuclear cells [2]. The inhibitor of the enzyme dipeptidyl peptidase IV, which degrades GLP-1, led to the decrease of TLR-2, IKKb expression and nuclear factor-kB (NF-kB) binding [3].

Due to these data L can influence NF-kB inflammatory cascade, but the mechanisms of anti-inflammatory activities of L remain to be determined. One possible way that L can influence an activity of some deacetylases because L modified an activity of Sirtuin 1(SIRT1) in several cell types in animal models [4-8]. On the other hand, recent evidences strongly suggest that SIRT1 up-regulation may serve as a potent therapeutic approach against development and progression of diabetic complications [9]. Taking together these data suggests that L can provide anti-inflammatory activity connected with an inhibition of NF-kB pathway mediated by up-regulation of SIRT1.

The aim of this study was to investigate L effects directed on pro-inflammatory NF-kB pathway

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and expression of SIRT1 in obese patients with type 2 diabetes mellitus (DM).

MATERIALS AND METHODS

This is a single-center, add-on prospective study. Fifteen obese patients with type 2 DM with a glycosylated hemoglobin (HbA1c) between 6.04 and 9.7% participated in this study. None of the subjects had any microvascular or macrovascular complications of diabetes. All patients were on stable doses of oral antidiabetic medications and had stable weight for 4 weeks before the study. All patients were on metformin (1–2 g/d), and 4 patients were on sulfonylureas (glymepiride 2 mg/d). The dose of statins and angiotensin converting enzyme inhibitors were not changed during the study. None of the subjects were on thiazolidinediones, antioxidants, or nonsteroidal anti-inflammatory drugs. Patients' demographic data are summarized in Table 1. All patients met with the dietitian and certified diabetes educator on 4 weeks before the study. General dietary recommendations as per American Diabetes Association guidelines were made to all subjects. All patients received L 1.2 mg daily add-on to stable therapy for 6 weeks. Blood samples were collected before, 6 weeks after start of treatment and 6 weeks after the stop of L after an overnight fast. The protocol was approved by the Ethic Committee of the University. An informed consent was signed by all subjects.

Table 1
Patient's demographic and clinical data at baseline, after 6 weeks of 1.2 mg liraglutide and 6 weeks after the stop of L

	Time points		
	Baseline	**At 6 weeks of L**	**At 6 weeks after the stop of L**
N (males)	15 (4)	15 (4)	15 (4)
Age (yr)	54.56±7.15		
Fasting glucose, mmol/L	8.46±1.80	6.73±1.05 P=0.0071	5.70±0.74 P=0.0001 P=0.0008
Systolic blood pressure, mm Hg	150.0±12.5	140.9±8.0 P=0.0015	137.7±6.8 P=0.0007 P=0.0669
Diastolic blood pressure, mm Hg	94.1±7.0	87.9±4.0 P=0.0015	86.8±4.6 P=0.0039 P=0.2578
Total cholesterol, mmol/l	6.62±1.34	6.07±0.74 P=0.0172	5.52±0.32 P=0.0069 P=0.0043
Ceruloplasmin, mg/l	253.92±16.54	236.38±16.09 P=0.0000	227.58±22.41 P=0.0002 P=0.0145

MNC isolation

Blood samples were collected in Na-EDTA and carefully layered on ficoll-urograpfine gradient. Samples were centrifuged and the MNC band was harvested and washed twice with Hanks' balanced salt solution. This method provides yields greater than 95% MNC in the preparation.

Quantification of TLR-2, TLR-4, NOD-1, TNFα, IL-2, IkB and SIRT1 expression

The mRNA expression of *TLR-2, TLR-4, NOD-1, TNFα, IL-2, IkB and SIRT1* was measured in MNC by RT-PCR. Total RNA was isolated using commercially available "RIBO-sole-C" (Inter LabService LTD, Russian Federation). Real-time RT-PCR was performed using D-256 (DNA-Technology, Russian Federation) system, kit for reverse transcription, Sybr Green Master Mix and gene-specific primers (Table 2) (Sintol, Russian

Table 2
Primer sequences for mRNA measurement

Genes	**Primers**
TLR4	F: 5'-AAGCCGAAAGGTGATTGTTG-3' R: 5'-CTGAGCAGGGTCTTCTCCAC -3'
TLR2	F: 5′-TCTCCCATTTCCGTCTTTTT -3′ R: 5′-GGTCTTGGTGTTCATTATCTTC -3′
SIRT1	F:5' - GCT GGC CTA ATA GAG TGG CAA - 3' R:5' - CTC AGC GCC ATG GAAAAT G - 3'
NOD1	F:5' - CTT CTG GTC ACT CAC ATC CGC A - 3' R:5' - TGG GCA TAG CAC AGC ACG AAC - 3'
β-actin	F:5' - ACC AAC TGG GAC GACATG GA - 3' R:5' - CCA GAG GCG TAC AGG GAT AG - 3'
IkBα	F: 5' - GGCTGAAGAAGGAGCGGCTA - 3' R: 5' - CCA TCT GCT CGT ACT CCT CG -3'
TNF-α	F:5' - AAC CTC CTC TCT GCC ATC AA - 3' R:5' - GGA AGA CCC CTC CCA GAT AG - 3'
IL-2	F:5' - CAA CTC CTG TCT TGC ATT GC - 3' R:5' - GCT CCA GTT GTA GCT GTG TT - 3'
GAPDH	F: 5' - GGC CTC CAA GGA GTA AGA CC - 3' R: 5' - AGG GGA GAT TCA GTG TGG TG - 3'

Federation). The expressions of *TLR-2, TLR-4, NOD-1, TNFα, IL-2, IkB and SIRT1* were detectable as $2^{-\Delta Ct}$. All the values were normalized to the expression of housekeeping genes action and GAPDH.

Plasma measurements

Glucose, ceruloplasmin and total cholesterol concentrations were measured in plasma by the photometric method. HbA1c concentration was measured by kits from BioSystems, Spain.

Statistical analysis

Statistical analysis was conducted using Sigma Stat software (SPSS Inc., Chicago, IL). All data are represented as mean ± SE. Paired *t* test and Student's *t* test were used where appropriate.

RESULTS

Baseline characteristics

Fifteen subjects received L – eleven females and four males, mean age 54.56 ± 7.15 yr; mean body mass index (BMI) 41.07 ± 6.38 kg/m^2 , mean HbA1c 7.79 ± 0.78% (Fig. 1), fasting glucose – 8.46 ± 1.80 mmol/L, total cholesterol – 6.62 ± 1.34 mmol/L, ceruloplasmin – 253.92 ± 16.54 mg/L. Patients had systolic blood pressure – 150.0+12.5 and diastolic blood pressure – 94.1 ± 7.0 mm Hg. Patients' baseline characteristics are summarized in Table 1.

Effect of L on metabolic indices

BMI decreased within 6 weeks of the administration of L 1.2 mg daily to 38.94 ± 4.93 kg/m^2 (p = 0.006) (Fig. 1,A). After the treatment with L, HbA1c fell significantly from 7.79 ± 0.78 to 7.12 ± 0.85 % (P = 0.0050) (Fig. 1, B), fasting glucose – from 8.46 ± 1.80 to 6.73 ± 1.05 mmol/L (P = 0.0071), total cholesterol – from 6.62 ± 1.34 to 6.07 ± 0.74 mmol/L (P = 0.0172), ceruloplasmin – from 253.92 ± 16.54 to 236.38 ± 16.09 mg/L (P = 0.0000). Blood pressure decreased significantly: systolic blood pressure – from 150.0 ± 12.5 to 140.9 ± 8.0 (P = 0.0015) and diastolic blood pressure – from 94.1 ± 7.0 to 87.9 ± 4.0 (P = 0.0015) mm Hg (Table 1).

At 6 weeks after the stop of L, BMI decreased from 38.94±4.93 to 37.62 ± 4.70 kg/m^2 (P = 0.0004), HbA1c fell significantly from 7.12 ± 0.85 to 6.66 ± 0.68% (P = 0.0030) (Fig. 1), fasting glucose – from 6.73 ± 1.05 to 5.70 ± 0.74 mmol/L (P = 0.0008), total cholesterol – from 6.07 ± 0.74 to 5.52 ± 0.32 mmol/L (P = 0.0043), ceruloplasmin – from 236.38 ± 16.09 to 227.58 ± 22.41mg/L (P = 0.0145). Blood pressure decreased insignificantly.

Effect of L on TLR-2, TLR-4, NOD-1, TNFα, IL-2, IkB and SIRT1 gene expressions

Peripheral blood MNCs had a relatively low expression of *TNFα* (0.11 ± 0.12)*, IL-2*(0.14 ± 0.2), *IkB* (0.06 ± 0.06*)* (Table 3), *TLR-2* (0.421 ± 0.126), *NOD-1* (0.047 ± 0.027), and *SIRT1* (0.008 ± 0.008) (Fig. 2 A, B, C, D) genes in comparison with the housekeeping gene.*TLR-4* gene expression was higher (1.658 ± 1.211).

Table 3

The mRNA expression of *TNFα, IL-2, IkB* at baseline, after 6 weeks of 1.2 mg liraglutide and 6 weeks after the stop of L

$2^{-\Delta Ct}$	Time points		
	Baseline	**At 6 weeks of L**	**At 6 weeks after the stop of L**
TNF-α	0.11 ± 0.12	**0.09 ± 0.09*** P=0.017241	**0.06 ± 0.07**$^{*, **}$ P=0.006536 P=0.005145
IL-2	0.14 ± 0.2	0.09 ± 0.16 P=0.069999	**0.06 ± 0.11*** P=0.035800 P=0.080778
IkB	0.06 ± 0.06	**0.04 ± 0.05*** P=0.005127	**0.04 ± 0.04*** P=0.043571 P=0.680863

After 6 weeks of treatment with L, *TLR-2* expression decreased significantly from 0.421 ± 0.126 to 0.286 ± 0.087 (P = 0.0000), *TLR-4* from 1.658 ± 1.211 to 1.125 ± 0.787 (P = 0.0011), *TNFα* from 0.11 ± 0.12 to 0.09 ± 0.09 (P = 0.017241)*, IkB* from 0.06 ± 0.06 to 0.04 ± 0.05 (P = 0.005127). *SIRT1* expression increased significantly from 0.008 ± 0.008 to 0.02 ± 0.01 (P = 0.000630). Expressions of IL-2 and NOD-1 were stable.

At 6 weeks after the stop of L, *TLR-2* expression still decreased significantly from 0.286 ± 0.087 to 0.195 ± 0.134 (P = 0.0451), *TLR-4* from 1.125 ± 0.787 to 0.439 ± 0.196 (P = 0.0020), *NOD-1* from 0.073 ± 0.072 to 0.014 ± 0.016 (P = 0.0063), *TNFα* from 0.09 ± 0.09 to 0.06 ± 0.07 (P = 0.005145). *SIRT1* and *IkB* expressions were stable. IL-2 expression decreased in comparison with basic level.

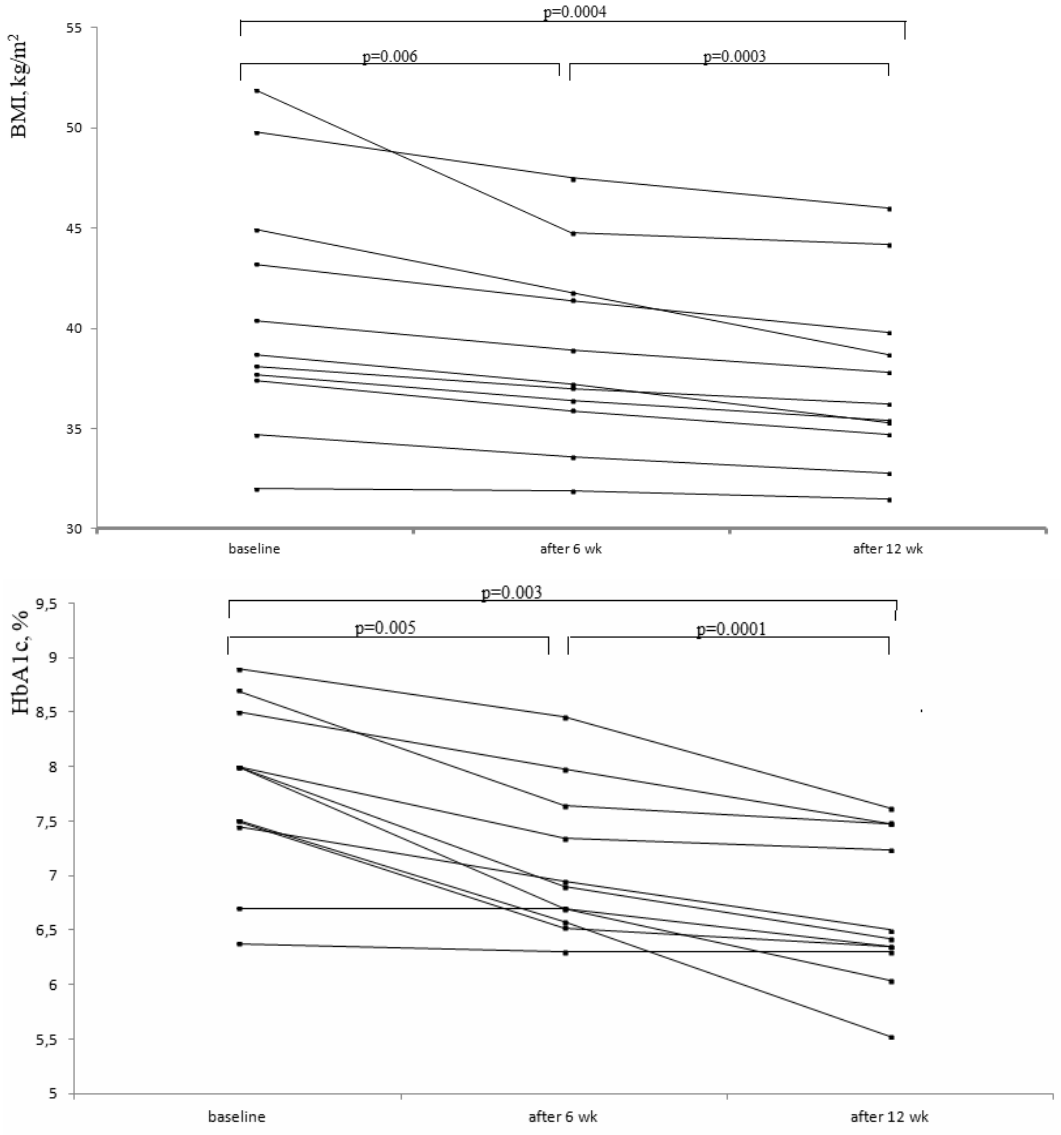
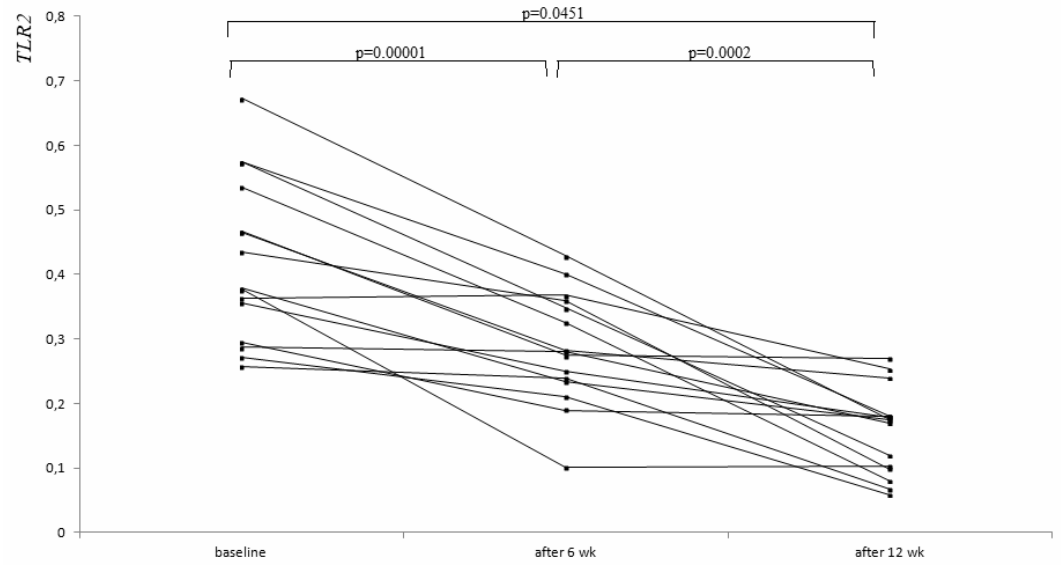


Figure 1. The mean values of BMI (A) and HbA1c (B) at baseline in obese Patients with Type 2 Diabetes, after 6 weeks of 1.2 mg liraglutide, and 6 weeks after the stop of liraglutide.



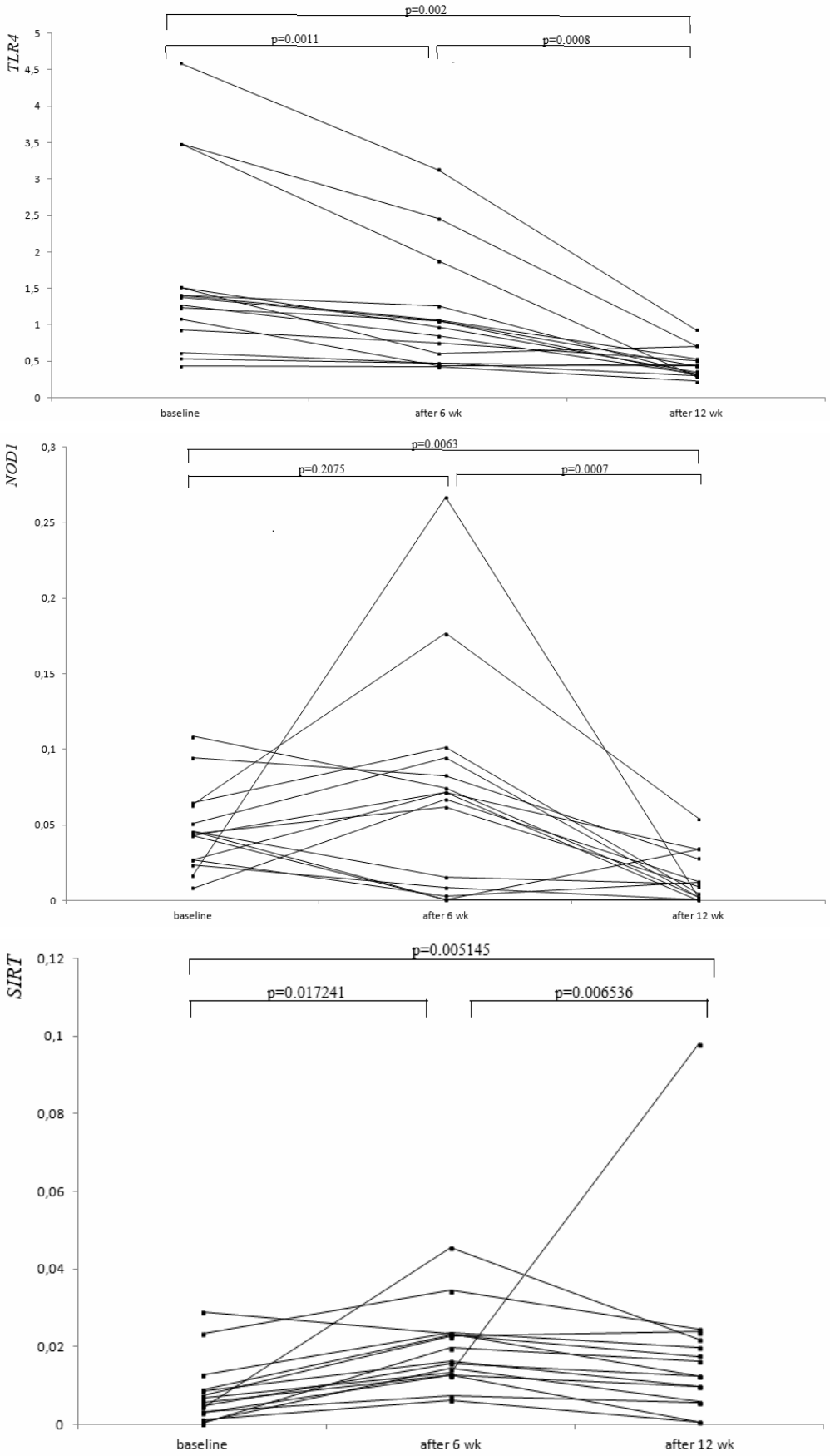


Figure 2. The mRNA expression of TLR-2 (A), TLR-4 (B), NOD-1 (C), and SIRT-1 (D) at baseline in obese patients with type 2 diabetes, after 6 weeks of 1.2 mg liraglutide, and 6 weeks after the stop of liraglutide. *y axis* – $2^{-\Delta Ct}$.

DISCUSSION

In this pilot clinical investigation we provided new data that L can inhibit proinflammatory NF-kB pathway by increased *SIRT1* expression in obese patients with type 2 DM improving metabolic profile.

Several years ago the conception for permanent activation of nuclear factor kB as a possible typical pathological process was provided supposing that NF-kB is the key molecule in the initiation and formation of "a vicious circle – insulin resistance – inflammation – atherosclerosis" [10].

An inflammatory process in the pathogenesis of insulin resistance in obesity and type 2 DM coupled to the IKKb/NF-kB pathway as a molecular mediator of insulin resistance and pharmacological target for insulin sensitization [11].

Our data support this point of view demonstrating that obese patients with type 2 DM had the high expression of *TLR-4*. TLR-4 is the receptor for endotoxin and some lipoproteins. Lipopolysaccharide-induced clinical inflammatory response were mediated by TLR-4 binding and led to the secretion of TNF-α. TNF-α is a NF-kB-induced gene product like IL-2, ceruloplasmin, etc.

Incretins or inhibitors dipeptidyl peptidase-IV (DPP-IV), such as exenatide, sitagliptin, liraglutide, are currently being used in the treatment of type 2 DM [12; 13; 14]. Inhibitor DPP-IV sitagliptine exerted a potent anti-inflammatory effect due to suppression of intranuclear NF-kB binding and the expression of IKKb, CCR-2, TLR-2 and CD26 [3].

GLP-1 suppressed inflammation (soluble intercellular adhesion molecule-1 and interleukin-6) in type 1 DM patients [15]. In animal model of allergic inflammation it was shown that GLP-1 inactivates NF-kB possibly through PKA [16].

L as GLP-1 analogue exerts an anti-inflammatory effect on vascular endothelial cells by increasing nitric oxide production and exerts anti-inflammatory action [12, 17]. L had a strong anti-inflammatory effect on cultured human aortic endothelial cells due to its ability to increase intracellular Ca^{2+} and activate CAMKKβ, which in turn activates AMPK [18].

Our data showed that L decreased the mRNA expression of TNF-α, *IkB, TLR2, TLR4,* in peripheral blood MNC. These findings support the anti-inflammatory activity of L directed to the NF-kB pathway and to the pattern recognition molecules.

TNF-α and TLR-4 induce serine phosphorylation of IRS-1 and are involved in insulin resistance pathogenesis [19]. Thus, L may be a potential insulin sensitizer. Recent data showed that liraglutide anti-inflammatory effects depended on *SIRT6* expression. Both endothelial progenitor cells and endothelial cells treated with high glucose (25 mmol/L) in the presence of GLP-1 (100 nmol/L liraglutide) presented a greater SIRT6 and a lower NF-kB expression as compared with cells treated only with high glucose. These findings establish the involvement of SIRT6 in the inflammatory pathways of diabetic atherosclerotic lesions and suggest its possible positive modulation by incretin, the effect of which is associated with morphological and compositional characteristics of a potential stable plaque phenotype [20].

From our point of view not only SIRT6 realized liraglutide effects but also SIRT1. Sirtuin 1 (SIRT1), a class III histone/protein deacetylase, is associated with aging and metabolism through maintaining inflammation via NF-kB. The up-regulation of NF-kB transcriptional activity and pro-inflammatory cytokine mRNA expression by p65 subunit of NF-kB and lipopolysaccharide were suppressed by SIRT1 [21]. Because of the central role of NF-kB in cytokine-mediated pancreatic β-cell damage, it was postulated that SIRT1 might work in pancreatic β-cell damage models [22].

As a deacetylase target of Sirt1, nuclear factor-kappa B (NF-kB) regulates the significant cell biological activity including cell cycle, apoptosis, adhesion and angiogenesis through interacting with its downstream genes [23]. It has been reported that Sirt1 could deacetylate p65 subunit of NF-kB at lysine 310 to inhibit its transcription physically [24].

In the animal models it was shown that L influenced SIRT 1 activity in obesity-induced chronic kidney injury [5], in TNF-a and hypoxia-stimulated H9c2 cells [6], in the infarcted heart [25], in non-alcoholic fatty liver disease [26], in streptozotocin-induced diabetic rats [7], and in the brain of type 2 diabetes rats [8].

Our data had shown the strong and long lasting effect of liraglutide on the expression of *SIRT-1* in patients. Liraglutide increased *SIRT-1* expression significantly after 6 weeks of treatment and this effect was observed during 6 weeks after the end of treatment. Moreover, we observed the further decreasing of BMI, HbA1c, fasting glucose, total cholesterol, and ceruloplasmin. Taking into consideration the fact that SIRT-1 is involved in the epigenetic regulation of pathological pathways in many diseases, such as type 2 DM [9, 26, 27], we suppose that such liraglutide effect is mediated by epigenetic regulation.

Our investigation has several limitations. The data obtained are limited by the add-on design of clinical investigation, and further placebo-controlled

trials are needed. A stronger calculation could be performed for statistical analysis to ensure the significance of L influence on *SIRT1* expression in obese patients with type 2 DM.

Recent data contributed to epigenetic treatment of type 2 DM targeted on SIRT1-regulated and relevant for diabetes genes by L. SIRT1-targeted L activity found in peripheral blood mononuclear cells should be proved in other metabolic active tissues in patients with type 2 DM. The tight control of NF-kB pathway by SIRT1 needs further investigations.

CONCLUSIONS

Liraglutide exerts an anti-inflammatory effect as reflected in decreasing of TNF-α, IkB, TLR2, TLR4, NOD1 mRNA within 6 weeks of treatment in peripheral blood mononuclear cells and over the period of 6 weeks after the end of treatment. Plasma ceruloplasmin, total cholesterol and fasting glucose concentrations also fall significantly. Long lasting effects of liraglutide can be mediated by epigenetic regulation of NF-kB pathway by SIRT-1. Liraglutide may therefore be potentially antiatherogenic and may have the ability of insulin sensitizer.

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Conflict of Interest disclosure: The authors declare that there are not conflicts of interest.

Introducere. *Ligaturidul (L) este un analog al hormonului glucagon-like peptide 1 ce stimulează secreţia de insulină dependentă de glucoză şi care poate să modifice expresia unor biomarkeri inflamatori. L poate influenţa cascada inflamatorie mediată de NF-kB dar mecanismele acesteia rămân încă neelucidate. Pe modele animale L influenţează activitatea Sirtuinei1 (SIRT1). Mai mult, studii recente arată faptul că supraexprimarea SIRT1 ar putea avea un rol terapeutic împotriva progresiei complicaţiilor diabetului. Scopul studiului a fost de a investiga efectele L asupra cascadei inflamatorii mediate de NF-kB şi SIRT1 la pacienţi obezi cu diabet zaharat tip 2.*

Materiale şi metode. *Au fost incluşi în studiu 15 pacienţi obezi cu diabet zaharat tip 2, toţi au avut iniţial tratament cu metformin şi sulfoniluree. Toţi pacienţii au primit L 1.2 mg/zi timp de 6 săptămâni. Au fost prelevate probe biologice înaintea iniţierii tratamentului cu L, la oprirea tratamentului şi la 6 săptămâni după oprirea tratamentului. Au fost izolate celulele mononucleate. Folosind tehnica RT-PCR, a fost analizată expresia ARN-ului mesager a TNF-α, TLR2, TLR4, NOD1, IL-2 şi SIRT1. Ceruloplasmina plasmatică a fost dozată prin metode spectrofotometrice.*

Rezultate. *L poate bloca activitatea NF-kB prin creşterea espresiei SIRT1 la pacienţii obezi cu diabet tip 2. Expresia ARNm a TNF-α, IkB, TLR2, TLR4 şi cea plasmatică a ceruloplasminei a scăzut după 6 săptămâni cu L. Expresia IL-2 şi a NOD nu s-au modificat. Expresia ARNm a SIRT1 nu a crescut. La 6 săptămâni după încetarea tratamentului cu L, expresia TNF-α, IkB, TLR2, TLR4, NOD1, SIRT1 şi a ceruloplasminei plasmatice nu s-a modificat spre valorile de bază. În schimb, nivelul IL-2 a scăzut comparat cu nivelul de bază.*

Concluzii. *L are un effect antiinflamator prin scăderea expresiei NF-kB şi creşterea expresiei SIRT1, scăzând expresia citokinelor pro-inflamatorii. Efectele de durată ale L pot fi explicate prin modificări epigenetice a căii NF-kB via SRT1.*

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