Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

The changes of inflammatory markers and irisine level in the first year of insulin therapy in type 2 diabetes patients

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Abstract. Objective: To evaluate the changes of inflammatory markers and irisine plasma level in the first year after initiation of insulin therapy in type 2 diabetes patients (T2DM). Material and Method: Twenty-three T2DM patients who started insulin therapy for better glycemic control were enrolled in our study. The study was conducted during the first year of insulin therapy and included 4 visits: initial visit, after 3 months, after 6 months, and after one year of insulin-therapy. Anthropometric and metabolic parameters (basal glycaemia, HbA1c, lipid profile) were measured at each visit, while adiponectin, interleukin-1β and irisin at the beginning, after 6 months and after one year of insulin therapy. Results: The mean age of the 23 patients was 62.30 ± 10.29 years, with a median duration of T2DM of 7 years (3-12 years). During the first year of insulin therapy the patients presented significant modification of HbA1c (10.23±1.94% versus 7.63±0.78%, $p<0.001$) and basal glycaemia (248.17±61.84 mg/dl versus 151.89±41.72 mg/dl, $p<0.001$), with significant increase in body weight and skeletal muscle mass, and no significant increase in body fat mass or percent of body fat. Adiponectin level was significantly lower after first year of insulin therapy: 7.06 mg/L (3.98;10.01) versus 4.81 mg/L (3.02;6.95), p=0.044; irisin level was significantly higher after one year of insulin therapy: 0.65 ng/ml (0.00;1.63) versus 1.37 ng/ml (0.57;1.70), p=0.004, with no significant change in circulating IL-1β levels: 5.45 pg/ml (3.54;7.22) versus 5.15 pg/ml (3.65;6.70), p=0.076. Conclusion One year after insulin therapy initiation, patients with T2DM showed a significant decrease in adiponectin levels, a significant increase in irisin levels and no significant changes in IL-1β levels.

Key Words: type 2 diabetes mellitus, insulin therapy, adiponectin, interleukin - 1β, irisin.

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Introduction

Despite multifactorial clinical management of the patient with type 2 diabetes mellitus (T2DM), nearly two-thirds of them die due to cardiovascular (CV) events (Herman et al 2017). The use of insulin therapy in T2DM patients was proved to be useful for significant reduction of microvascular complications in landmark randomized clinical trials such as UKPDS (United Kingdom Prospective Diabetes Study) due to an intensive and sustained glycemic control (UKPDS Group 1998), even though initial data showed no reduction in macrovascular risk. The follow-up of these patients has shown that the initial glycemic control offered further protection for microvascular complications, while subsequently published data showed that intensive glycemic control at the onset of T2DM had long-term benefits regarding macrovascular complications (Holman et al 2008). But in real-life management of T2DM, the majority of patients receiving insulin therapy are those with older duration of the disease and important comorbidities, which are by themselves risk factors for adverse effects (Ferrannini & DeFronzo 2015). In ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial, the use of insulin in T2DM patients with cardiovascular disease (CVD) or CV risk factors showed no safety concerns regarding mortality or CVD events (Gerstein et al 2012). On the other hand, Gamble et al observed a significant and graded association between level of exposure to insulin and CV and non-vascular mortality (Gamble et al 2010). These findings were also supported by the observations from ACCORD study (which was stopped due to increased mortality in the arm with intensive glucose control) (Riddle et al 2010) and by further analysis of Bonds et al, which showed a proportionally increased risk for higher insulin dose (Bonds et al 2010). Therefore, the published results about the effect of insulin on CVD and mortality have contradictory results and methodological limitations, no final conclusion being provided regarding risk-benefit of insulin therapy in T2DM. (Muis et al 2005; Asleh et al 2017). Beyond antihyperglycaemic action, insulin has pleiotropic effects. In vitro studies proved that insulin has anti-inflammatory and anti-atherogenic effect (Dandona P et al 2009). Its action on vascular endothelium leads to nitric-oxide release and vasodilatation (Grover A et al 1995) and has a suppressive effect on the expression of NFkappaB and MCP-1 in human endothelial cells (Aljada et al 2001).

Adiponectin is a major cytokine secreted by adipose tissue, which has been shown in fundamental studies to play an important role in glucose metabolism by reducing insulin resistance and inflammation (Kadowaki et al 2006). High plasma concentration of adiponectin was linked with lower risk of T2DM (Nicholson et al 2018; Yamamoto et al 2014) and its serum level was inversely correlated with weight and central obesity in humans, regardless of diabetic status (Nayak et al 2010). In patients with T2DM, adiponectin level is lower than in non-diabetic controls and its levels were negatively correlated with insulin resistance and adiposity (Aleidi et al 2015; Nayak et al 2010). There is a crosstalk between adiponectin and insulin: the adipokine has an insulin-sensitizing action, due to muscle microvasculature dilatation, with increasing delivery of insulin to muscle cells (Zhao et al 2014), but there are little evidence regarding the effect of insulin therapy on adiponectin levels in T2DM.

Irisin is a newly discovered myokine, whose secretion is influenced by (PGC1) -α (peroxisome proliferator-activated receptor-α coactivator-1) (Huh et al 2012). Irisin has been proposed as the mediator of beneficial effects of physical exercise on metabolism by increasing thermogenesis due to a browning process of the white fat (Boström et al 2012). The response of genes encoding irisin after exercise is different depending on age, higher increase in the elderly than in young, but lower circulating levels of irisin due to reduced muscle mass in the elderly (Timmons et al 2012). Thus, the circulating level of irisin is inversely proportional to the circulating level of adiponectin and direct proportionally with body mass index (BMI), basal glycaemia and total cholesterol (Enerback 2010).

Since contradictory literature data regarding the response of inflammatory markers in patients with T2DM treated with insulin is reported, and since so far, few data of insulin therapy effect on irisin levels were reported, our aim was to conduct a personal research in order to assess the impact of insulin therapy initiation on inflammatory markers, adiponectine and on irisin plasma level in T2DM patients.

Material and method

We conducted a cohort study that included patients with prior diagnosis of T2DM who needed initiation of insulin therapy for better glycemic control. All patients received basal insulin therapy with glargine (Lantus, Sanofi). The study was conducted during the first year of insulin therapy and included 4 visits: initial visit, after 3 months, after 6 months, and after one year of insulin therapy. The study was approved by the Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca.

At the initial visit, the patients received informations about the study and the Informed Consent was signed. We collected information about patients' data: age, gender, duration of diabetes, current treatment, complications, blood tests (glycaemia, HbA1c, creatinine, transaminase, LDL cholesterol, HDL cholesterol, triglycerides, irisine, adiponectin, interleukin 1-beta). During this visit patients received information about lifestyle optimization and were trained in insulin injection and blood glucose monitoring technic, received information about insulin dose adjustment algorithms and about hypoglycemia management. Afterwards, during subsequent visits, the procedures for the initial clinical and paraclinical measurements were performed. Adiponectin, IL-1β and irisin levels were measured at initial visit, after 6 months and after 12 month after the initiation of insulin therapy. The body composition analysis was performed during every visit, using InBody 720 device (Biospace Co., Korea) according to the recommendation provided in the user manual (InBody 720 User's Manual, Biospace 1996-2004). This analysis was derived from the four compartment model, which divides body composition into four components: total body water, protein, mineral and body fat mass.

After prelevation, blood samples (5 mL) were collected using pyrogen-free tubes without anticoagulant. Samples were immediately centrifuged at 3000 g, for 10 min at 4 °C. Serum was separated in Eppendorf tubes and frozen at -80 °C until analysis. The serum levels of irisin, adiponectin and IL 1 (Abbexa USA kits) were measured using the enzyme-linked immunosorbent assay ELISA using commercially available reagents. The standard dilutions and samples preparation was performed according to the manufacturer's instructions.

Statististical analysis was performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Quantitative data were tested for normality of distribution using the Kolmogorov-Smirnov test, and were expressed by mean and standard deviation or median and 25-75 percentiles. Comparison between measurements was performed using ANOVA for repeated measures or Friedman test, whenever appropriate. A p value <0.05 was considered statistically significant.

Results

Twenty-five patients were enrolled in the study, of which 23 patients reached the final visit (7 women, 30.4%), while two were excluded from the study (the first one was excluded because he did not attend all protocol visits while the second patient discontinued insulin therapy before the final visit). The mean age of the 23 patients remaining in the study was 62.30 ± 10.29 years, with a median duration of T2DM of 7 years (3-12 years). Despite the metabolic imbalance, only 8 patients (34.78%) reported a weight loss prior to initiating insulin therapy, with values ranging from 2 to 15 kg. The initial insulin dose was 18.96 ± 6.32 units/day, and the final visit dose was 33.34 ±18.66 units/day. Regarding associate treatment, 21 patients (91.3%) received metformin, 16 patients (69.6%) were treated with angiotensin inhibitors, 1 patient (4.3%) with sartans, 8 (34.78%) with beta-blockers, 16 (69.6%) received statin therapy, and 5 patients (21.7%) had fenofibrates.

The evolution of clinical and paraclinical parameters is shown in Table 1. After the first year of insulin therapy the patients presented a significant improvement of parameters regarding glycemic control. HbA1c and basal glycaemia decreased progressively after first year of insulin therapy from 10.23±1.94% to 7.63±0.78% ($p<0.001$) and from 248.17±61.84 mg/dl to 151.89±41.72 mg/dl, respectively. Twenty patients (86.95%) presented weight gain, being observed a significant increase in body weight ($p=0.005$), with a median value of 2.4 kg (1.6; 5.5), but with no significant increase in body fat mass or percent of body fat. A significant increase of HDL-cholesterol and decrease of triglycerides was also recorded.

Adiponectin level was significantly reduced after one year comparative with initial level, while irisin presented significantly

Table 1. The evolution of clinical and paraclinical parameters during one year, after insulin therapy initiation

Parameter	Initial visit N=23	3 month visit N=23	6 month visit N=23	12 month visit N=23	p
HbA1c (%)	10.23±1.94	8.12±1.36	7.76±1.15	7.63±0.78	<0.001
BG (mg/dl)	248.17±61.84	157.97±61.36	167.84±39.39	151.89±41.72	<0.001
Weight (kg)	83.26±14.04	83.99±13.50	85.31±13.81	86.16±14.43	0.005
BMI (kg/m²)	29.8 (27.00;32.70)	30.4 (27.90;32.60)	30.9 (28.00;32.90)	31.6 (27.80;33.40)	0.01
PBF (%)	32.94±10.63	32.13±9.62	32.81±9.23	33.45±9.82	0.262
VFA (cm²)	137.66±39.87	141.23±36.79	138.53±32.62	141.91±37.37	0.608
SMM (kg)	31.00±7.15	31.66±7.11	31.85±7.51	31.97±7.54	0.005
BFM (kg)	28.3 (21.10;33.20)	27.2 (20.40;32.60)	27.2 (21.70;33.60)	27.5 (22.90;35.30)	0.128
SBP (mmHg)	142.91±20.74	145.21±16.02	138.65±16.43	142.60±16.51	0.434
DBP (mmHg)	82.17±9.43	82.65±9.87	83.34±10.07	81.69±10.87	0.904
TC (mg/dl)	196.87±69.86	170.84±44.12	176.14±43.37	184.22±49.77	0.16
LDL-chol (mg/dl)	112.05±54.61	94.07±34.50	100.88±38.96	102.73±42.57	0.33
HDL-chol (mg/dl)	39.03±12.59	44.55±15.37	43.17±12.12	44.18±13.02	0.012
Triglycerides (mg/dl)	180 (121;303)	159 (106;191)	146 (102;204)	145 (107;256)	0.014

N- Number of patients; BG – basal glycaemia; BMI – body mass index; PBF – percent body fat; VFA – visceral fat area; SMM – skeletal muscle mass; BFM – body fat mass; SBP – systolic blood pressure; DBP-diastolic blood pressure; TC-total cholesterol; LDL-chol – low-density lipoprotein cholesterol; HDL-chol – high-density lipoprotein cholesterol.

Table 2. Adiponectin, IL-1β and irisin level evolution after insulin therapy initiation

Parameter	Initial visit N=23	6 month visit N=23	12 month visit N=23	p
Adiponectin (mg/L)	7.06 (3.98;10.01)	7.44 (5.07;10.85)	4.81 (3.02;6.95)	0.044
IL-1β (pg/ml)	5.45 (3.54;7.22)	4.71 (2.65;6.33)	5.15 (3.65;6.70)	0.076
Irisin (ng/ml)	0.65 (0.00;1.63)	1.60 (0.99;1.84)	1.37 (0.57;1.70)	0.044

increased levels after the first year of insulin therapy, with no significant modification in IL-1β circulating levels (Table 2).
Stratification for insulin dose showed a progressively significant reduction of adiponectin level after one year of insulin therapy in patients with more than 0.3 units of insulin/kg body weight/day (p=0.019), but with no significant reduction in patients with less than 0.3 units of insulin/kg body weight/day.
The circulating levels of IL-1β presented significantly lower levels after one year of insulin therapy (p=0.038) in patients which had lower initial levels of LDL-cholesterol. The other factors like age, gender, T2DM duration, initial BMI, body composition parameters, associated treatment or insulin dose had no significant influence on IL-1β levels.
Regarding the circulating levels of irisin, a significant increase was observed in patients treated with fenofibrate (p=0.001). Other factors like age, gender, T2DM duration, initial BMI, body composition parameters, insulin dose, adiponectin and IL-1β levels were not influencing irisin levels.

Discussions

Despite the anti-inflammatory effect of insulin, in patients with T2DM, insulin therapy appears to increase oxidative stress and inflammatory markers (Palem & Abraham 2015), with a direct correlation to insulin dose. In a recent published study, the level of high-sensitivity C-reactive protein was significantly increased in the third tertile of insulin dose/body weight, compared with the first tertile (Bala et al 2018). Accordingly, the interleukin-1 (IL-1) cytokine family is linked to inflammation-related diseases, including T2DM, while IL-1β, in particular, has been shown to be a target for reducing inflammation with potential therapeutic benefits (Donath et al 2009). This hypothesis was confirmed by the recently published results of the Phase III Cantos Study (The Canakinumab Anti-inflammatory Thrombosis Outcomes Study) involving 10.061 patients. Among patients, (approximately 40% with T2DM with a history of myocardial infarction and C-reactive protein ≥ 2 mg/dl), the anti-inflammatory therapy targeting IL-1β proved to reduce recurrent CV events compared to placebo, regardless the level of lipids (Ridker et al 2017).

Within our study, the variation of IL-1β during insulin treatment was insignificant, with no significant difference between the initial and the final values. Even though, initially, we observed a decrease in IL-1β levels, afterwards its level increased and the difference became insignificant after the first year of insulin therapy. We already know that acute administration of insulin leads to an initial decrease in inflammation markers (Dandona et al 2001). By reducing metabolic stress induced by hyperglycemia and direct suppression of proinflammatory cytokines, insulin potentially plays an anti-inflammatory role (Sun et al 2014). Considering these, although inflammation increases insulin resistance, there was no correlation between IL-1β level and total insulin dose in our study.

Adiponectin and inflammatory markers are related with insulin mediated turnover of the glucose (Nayak et al 2010). Adiponectin plays an important role in glucose metabolism by increasing muscle glucose uptake and insulin-sensitivity, by a direct vasodilatatory effect on muscle microvasculature (Zhao et al 2014). In our study, a non-significant increase was observed after six months of insulin therapy, in contrast with Wang et al study, where a significant increase was observed in the same period of time (Wang et al 2015). In another study, a significant increase of adiponectin occurred in a cohort of 84 Chinese patients with T2DM after 3 months of insulin therapy, but no further increment was observed at 12 months (Zhang Q et al 2016). Up to a point, the same results were observed in both studies: an increase in adiponectin levels after 6 months of insulin therapy initiation, even though in our study the results were statistically insignificant, but in contrast in our study a significant decrease in the circulating level of adiponectin after the first year of insulin therapy was noticed. Further, the same process of adiponectin decrease was observed in a different study published by Fujita et al (2005). This phenomenon of insulin suppression on adiponectin was observed in mice, process explained by the hyperinsulinemic status caused by exogenous administration of insulin (Fujita H et al 2005). Similarly, in our study, the progressive and significant decrease of the adiponectin occurred in patients with a higher dose of insulin (more than 0.3 units of insulin/kg body weight/day). This phenomenon is explained by the fact that the low level of adiponectin decreases the oxidation of free fatty acids, and by this increasing their circulating level and insulin resistance. Consequently, higher doses are needed for glycemic control (Sheng & Yang 2008).

Irisin is a myokine discovered in 2012 by Boström et al which has the ability to turn certain types of white tissue into brown tissue, potentially promoting weight loss by increasing thermogenesis, with a beneficial role in reducing insulin resistance (Boström et al 2012). The presence of irisin's precursors in adipose tissue suggests that it can also be an adipokine (Roca-Rivada et al 2013; Moreno-Navarrete et al 2013). Also, a recently published study on irisin highlighted that irisin can be an independent risk biomarker of CV disease in T2DM; the lower levels increasing by 1.6 fold the risk for CVD (El-Lebedy et al 2018). The physical activity, the high protein diet and some drugs like metformin, insulin, exenatide, simvastatin and fenofibrate treatment have a positive effect on irisin circulating levels, while the presences of obesity have a negative effect, lowering irisin levels (Mahgoub et al 2018).

Within our study, the circulating levels of irisin increased significantly after the first 6 months, afterwards starting to decrease. Its variation between the initial and final moment of insulin therapy remained significantly different. Also a significant increase in irisin levels was observed in patients treated with fenofibrate. This effect was also observed in mice study, and the explanation is that PPAR-α activation produced by fenofibrate stimulates formation of beige cells in subcutaneous white adipose tissue (Rachid et al 2015). On the other hand in patients with T2DM and hypertriglyceridemia, administration of fenofibrate decreases irisin levels, probably due to the reduction of irisin resistance (Feng et al 2015). Generally, irisin levels are lower in T2DM patients as compared with control group and no correlations with anthropometric or metabolic parameters were found (Liu et al 2013). These findings are supported by our study as well, since no significant clinical or metabolic parameter influencing the irisin level was found.

Conclusions

The initiation of insulin therapy in people with T2DM is associated with a significant decrease in adiponectin and a significant increase in irisin after the first year of insulin therapy. The circulating IL-1β level was not significantly modified. For a better understanding of the role and influence of adiponectin, IL-1β and irisin in T2DM disease, further studies including a larger number of patients and a bigger follow up period are necessary. Also, more research studies should be focused on the potential use of irisin as an independent risk biomarker of CV disease in T2DM. The correlation of the adiponectin level with the dose of insulin can be explained by the fact that the low level of adiponectin decreases the oxidation of free fatty acids, and by this increasing their circulating level and insulin resistance. Considering this, the increase of insulin resistance can mask the anti-inflammatory effect of the insulin observed in other studies.

Conflict-of-interest statement

Anca-Elena Crăciun declares speaker fees, sponsorships and consultancy fees from AstraZeneca, Sanofi, Eli Lilly, Servier, Merck Sharpe&Dhome, Mylan, Novo Nordisk, Amgen.

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Citation	Crăciun CI, Crăciun AE, Vesa S, Pop RM, Bocșan CI, Buzoianu AD. The changes of inflammatory markers and irisine level in the first year of insulin therapy in type 2 diabetes patients. HVM Bioflux 2018;10(2):79-84.
Editor	Antonia Macarie
Received	17 May 2018
Accepted	6 June 2018
Published Online	28 June 2018
Funding	None reported
Conflicts/ Competing Interests	None reported