

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Inflammatory Markers Associated with Chronic Hyperglycemia and Insulin Resistance

Margina Denisa

University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest, Romania

1. Introduction

Chronic hyperglycemia associated with type 2 diabetes mellitus (T2D) is a result of deficient insulin secretion and/or resistance of target tissues to insulin's action. Chronic hyperglycemia is a major etiological factor causing both micro- and macrovascular lesions associated with diabetes. Numerous biochemical changes initiated by hyperglycemia directly influence cellular function and lead to abnormal vascular remodeling and the development of vascular diabetic complications (Wadham et al., 2007, King et al, 1996, Brownlee, 2001).

Recent literature data states that the innate immune system might be involved in the pathogenesis of type 2 diabetes. It is now commonly accepted that diabetes is associated with low-grade inflammation; there are a lot of human studies that demonstrate an increase for some of the inflammatory markers (hsCRP) including interleukins (IL-6, etc) and several adhesion molecules (intercellular adhesion molecule 1, ICAM-1, E-selectin) in patients with T2D, compared to controls (Garcia et al, 2010). Type 2 diabetes is initiated as a result of both genetic and acquired individual factors associated with triggering stimuli such as overeating, under-activity, increasing age, psychological stress and smoking. All these are also responsible for the activation of innate immunity, leading to insulin resistance (Garcia et al, 2010).

Obesity induces changes in skeletal muscle, adipose tissue and the liver that result in localized inflammation and insulin resistance (IR) through autocrine and paracrine signaling. Excess adiposity is the most important risk factor for the development of insulin resistance, type 2 diabetes and their cardiovascular complications (Tataranni, 2005). Insulin resistance is extensively studied by medical and scientific communities because of its increased prevalence and its association with cardiovascular disease. Even if the precise molecular mechanism(s) linking insulin resistance to the development and/or progression of atherosclerosis remains under debate, it is clear that inflammation is a contributing factor. The exact physiological events leading to the initiation of the inflammatory response in obesity remain incompletely understood. Adipokines such as resistin and leptin, which are secreted by adipocytes, can induce inflammation and the associated insulin resistance. As part of the chronic inflammatory process, chemokines secreted locally, in the adipose tissue, attract pro-inflammatory macrophages that contribute to the acceleration of inflammatory markers' synthesis (Zavaroni I, 2000, De Luca 2008).

Adiponectin is one of the adipocyte-derived proteins that have insulin-sensitizing, antiinflammatory, and antiatherogenic properties. Clinical studies show that decreased plasma levels of adiponectin have been associated with obesity, type 2 diabetes, and hypertension; plasma adiponectin levels are significantly lower in patients with coronary artery disease. Experimental as well as clinical studies strongly suggest that physiologic levels of adiponectin are necessary to maintain the normal, non-inflammatory phenotype of the vascular wall and that the protective role of adiponectin is due to its capacity to preserve the endothelial cell function (Ouedraogo et al, 2007, Goldstein & Scalia, 2004, Scherer, 2006, Arita et al, 1999, Hotta et al, 2000, Iwashima et al, 2004, Ouchi et al, 2000).

Relative risk of cardiovascular disease is increased 2–3 times in diabetic men and 3–4 times in diabetic women compared to non-diabetic controls; atherosclerosis is the major causal factor for these pathological events (Ray et al, 2009). Blood-borne inflammatory and immune cells constitute an important part of the atheroma lesions; activated immune cells in the atherosclerotic plaque produce inflammatory cytokines (interferon γ , interleukin-1, and tumor necrosis factor), which induce the production of substantial amounts of interleukin-6 (IL6) and other inflammatory factors (Hansson, 2005). Therefore inflammation is an important component in the development of atherosclerosis specifically in the setting of type 2 diabetes and insulin resistance.

In patients at high risk of cardio-vascular disease, the first signs of endothelial dysfunction are observed in morphologically intact vessels, before the onset of clinically manifested vascular disease. There are several lines of evidence indicating especially that endothelial function is compromised in situations associated with reduced sensitivity to endogenous insulin. The adhesion of circulating leukocytes to endothelial cells plays an important role in the initiation of atherosclerosis. Cellular adhesion molecules are poorly expressed by the resting endothelium, but they are up-regulated during atherogenesis; the soluble forms of some cellular adhesion molecules, such as E-selectin, can be found in plasma and it has been suggested that elevated plasma levels of these cellular adhesion molecules may constitute an index of endothelial activation or even a molecular marker of early atherosclerosis (Ceriello, 2004, Stühlinger, 2002). Adhesion molecules (E-selectin, ICAM1, VCAM) as well as cytokines are up-regulated under the effect of hyperglycemia (Zheng et al, 2007, Miyamoto et al, 1999, Joussen et al, 2002).

Nitric-oxide (NO) is synthesized from L-arginine by a family of enzymes, called NO synthases (NOSs) and has antiatherogenic and antithrombotic functions. The constitutively expressed NOS isoforms, endothelial NOS (eNOS) and neuronal NOS (nNOS), are likely to be the major contributors to whole-body NO production. In the last decades, a great effort has been made to understand the role of NO as a modulator of physiological insulin secretion as well as its ability to modulate glucose metabolism and its involvement in insulin resistance. It has been described that eNOS activation, specifically localized in skeletal muscles, increases muscle blood flow, with increased delivery of glucose to the muscle cell (Monti L.D., 2003). In endothelial cells, insulin stimulates the expression and activity of endothelial NO synthase (eNOS), resulting in increased production of NO. Under normal circumstances, NO is not only critically important in the process of vasodilatation, but it also counteracts the stimulatory effect of VEGF on the expression of adhesion molecules such as E-selectin, intracellular adhesion molecule (ICAM1), and vascular cellular adhesion molecule (VCAM), thereby protecting the endothelial cells from excessive interactions with circulating monocytes (Low Wang, 2004).

Endothelial dysfunction is associated with many pathological conditions, including hyperlipidemia, hypertension, metabolic syndrome, insulin resistance and diabetes.

Endothelial dysfunction is characterized by a loss of nitric oxide bioavailability mainly due to its inactivation under the effect of superoxide excessively produced and is considered a very important cellular event responsible for the adverse effects of high glucose on the blood vessels (Wadham et al, 2007, Brownlee, 2001). Both in vitro and in vivo studies show that exposure to hyperglycemia reduces endothelial NO availability and its bioactivity (Williams et al, 1998, Veves et al, 1998).

The control of blood glucose homeostasis is mainly determined by two closely related physiological mechanisms: the capacity of the pancreas to secrete insulin and the biological action of this hormone on insulin-sensitive tissues, especially liver, muscle and adipose tissue (Foss-Freitas, 2004). It is well known that in type 2 diabetes mellitus and in metabolic syndrome, as well as in various other human pathological states such as glucose intolerance, obesity, polycystic ovary syndrome, essential hypertension, and, more recently, atherosclerosis, insulin resistance is either an associated condition or is considered to be a predictor or pathogenic factor (De Fronzo, 1988, 1991, Guizea, 2008). Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal physiologic response in the main target tissues of the pancreas hormone (fat, muscle, liver).

Insulin resistance reduces the effects of insulin and results in elevated hydrolysis of triglycerides stored in the fat cells, leading to an increase of the free fatty acids' level in plasma. Insulin resistance in muscle cells reduces the glucose uptake, whereas in liver cells results in impaired glycogen synthesis and a failure to suppress glucose production. All these phenomena lead to reduced muscle glucose uptake and increased liver glucose production, thus contributing to the elevation of the blood glucose level, and accelerating the glucose toxicity associated with the insulin resistance (Freitas 2004, De Fronzo 1988, 1991, Guizea 2008).

The medical community agrees that the evaluation of the insulin resistance phenomena might be important for the assessment of hyperglycemia patients. According to literature data, the most efficient and scientifically correct methods for the evaluation of insulin resistance are "clamp" techniques. These procedures require i.v. access, multiple venipunctures, and take a long time, thus being relatively impractical for office assessment and difficult from the patients' point of view. The euglycemic hyperinsulinemic clamp technique is the reference method, the "gold standard" for quantifying insulin sensitivity or resistance in vivo because it directly measures the effects of insulin on glucose use under steady state conditions (Freitas 2004). Besides the euglycemic hyperinsulinemic clamp technique, other clamp techniques have been developed: frequently sampled IV glucose tolerance test (FSIVGTT), insulin tolerance test (ITT), insulin sensitivity test (IST), and continuous infusion of glucose with model assessment (CIGMA). There are also some models available for the evaluation of insulin resistance depending on glucose and insulin levels in oral glucose tolerance tests: Insulin Sensitivity Index (ISI), Matsuda test, Caderholm test, Gut test, etc. Unfortunately, most of these methods share the disadvantages of the euglycemic hyperinsulinemic clamp, requiring i.v. access, multiple blood sampling, glucose/insulin infusion for several hours, being also difficult to use for the patients and for the specialists (McAuley 2001, Matsuda 2010).

Largely because of the fact that the standard methods for assessing beta-cell function and insulin sensitivity, the hyperglycemic and euglycemic glucose clamps, are complex and costly to perform, several studies have been conducted to determine simpler and more applicable assessments (Dansuntornwong 2007).

So the mathematical models for the evaluation of insulin resistance depending on fasting levels of glucose and insulin are presently used. The most popular test of this kind is the Homeostatic model assessment (HOMA) of β -cell function and insulin resistance and it was first described in 1985 (Soonthornpun 2003). This test represents a method for assessing β -cell function and IR from basal glucose and insulin or C peptide concentrations. The model has been widely used since it was first published. (Wallace 2004, Song 2007, Margina 2005).

Recent data mentioned some other models for the evaluation of insulin resistance. Quantitative Insulin Sensitivity Check Index (QUICKI) can be evaluated depending on fasting levels of glucose and insulin. Many investigators believe that QUICKI is superior to HOMA as a way of determining insulin sensitivity (Katz 2000, Mather 2001, Yokoyama 2000).

Since T2D, obesity, insulin resistance, metabolic syndrome, and atherosclerosis, the last one being the main complication of chronic hyperglycemia, share the inflammatory pattern, the aim of this research was to assess the profile of some markers of inflammation (hsCRP, IL6, E-selectin), of the adipocyte function (adiponectin) and of the endothelial status (plasma NO stable end products) in correlation with the insulin resistance indexes, in a Romanian group of patients.

For this purpose 80 patients were selected and their informed consent was obtained. Any past or present insulin treatments, along with hematological, kidney or malignant diseases were exclusion criteria.

2. Materials and methods

2.1 Subjects and study design

We included in our study 80 patients, 40 to 60 years old. Any past or present insulin treatment, along with any hematological or kidney diseases were an exclusion criterion. The protocol was approved by the local ethics committee and the informed consent of the patients was obtained.

2.2 Biochemical evaluation

For the studied patients we assessed, on *à jeun* blood samples, the following parameters: fasting plasma glucose (FPG), fasting plasma insulin, plasma lipids and lipoproteins (total cholesterol - TC, triglycerides -TG, low density lipoproteins - LDL, high density lipoproteins - HDL), plasma insulin level. Fasting plasma glucose and plasma lipids (TC, LDL, and HDL) were determined using automatic devices and commercial kits (Merck and Biorad), on an Olympus 400 analyzer. Insulin, adiponectin, interleukin 6 and E-selectin were evaluated using ELISA kits (Invitrogen) on a ChemWell 1000 device. The NO stable end products (nitrite and nitrate) were evaluated using enzymatic catalysis coupled with Griess reaction (Gradinaru, 2003, Moshage, 1995, Archer, 2003)

Using the values of fasting plasma glucose and insulin, several insulin sensitivity indexes have been evaluated (Quicki, HOMA-IR, $1/\text{HOMA-IR}$, $\log(\text{HOMA-IR})$, HOMA-B), according to the presented formula (McAuley 2001, Matsuda 2010, Dansuntornwong 2007, Wallace 2004).

2.3 Statistical analysis

Results are reported as means \pm standard deviation (SD). Student *t* test was appropriately used for group comparisons. Correlations were assessed by a non-parametric test (Spearman). P values <0.05 were considered statistically significant.

3. Results an discussions

The patients were divided into three groups, according to their BMI:

- control group (n=20), BMI<25 kg/ m²,
- overweight group (n=30), 25 kg/ m²≤BMI<30 kg/ m²,
- obese group (n=30), BMI≥30 kg/ m².

Table 1 shows the general biochemical parameters for the three studied groups.

Our results show that the weight increase is associated with a disturbance of the glycemic and lipid homeostasis. The fasting plasma glucose, total cholesterol and the lipoprotein levels increased from the control group to the other two studied groups. The LDL and TG increased significantly at the obese patients compared to controls, but not significantly at overweight patients compared to controls. All the other parameters varied significantly both in the overweight and the obese groups compared to the lean group.

Evaluated parameters	Control group	Overweight group	Obese group
BMI (kg/ m ²)	21.46±2.02	27.28±1.61**	35.04±4.74**
Fasting plasma glucose (mg/ dL)	85.8±7.25	128.2±74.17**	163.24±73.80**
Total cholesterol (mg/ dL)	176.60±34.46	201.05±38.48*	216.8±37.11**
LDL cholesterol (mg/ dL)	100.18±39.10	119.48±37.18	133.51±30.72*
HDL cholesterol (mg/ dL)	60.20±13.17	48.47±11.34*	48,80±15.52*
Triglycerides (mg/ dL)	81.10±55.67	86.75±52.61	173.36±129.21**

*p<0.05, **p<0.01

Table 1. The biochemical parameters for the overweight and obese patients compared to the control group

Analyzing the lipid profile of the selected patients we pointed out that 36% of the overweight and 45.5% of the obese group were hypercholesterolemic (TC>220mg/ dL). The HDL level did not meet the cardioprotective (>45mg/ dL) level for 29% of the overweight and 54.5% of the obese patients.

So, the analysis of the glucose and lipid markers only shows an increased risk of atherosclerotic events for some of the patients in the obese and overweight groups but does not allow identifying the mechanism involved in the potential endothelial lesions.

Since the discovery of adiponectin, numerous studies have supported the theory that adiponectin has similar action with insulin and increases the pancreatic hormone’ metabolic function, as well as its anti-atherogenic properties; animal studies also suggest that adiponectin may exert a protective role in vascular homeostasis. In humans, plasma levels of adiponectin are negatively correlated with adiposity, and decreased plasma adiponectin levels are also observed in patients with diabetes, as well as in subjects with diseases caused by impairment of the endothelial function. Since adiponectin is secreted exclusively from adipose cells, deregulation of adiponectin synthesis and action may provide a link between obesity, insulin resistance, diabetes, vascular complications of diabetes and atherosclerosis (Arita et al, 1999, Hotta et al, 2000, Iwashima et al, 2004, Ouchi et al, 2000). So adiponectin, as well as the endothelial derived relaxing factor (NO), have anti-atherogenic properties. The imbalance of these two markers caused by the weight increase is associated with a general

impairment of the vascular function and with a loss of the glycemic, lipid and lipoproteic control.

Statistical analysis of the recorded data revealed that the adiponectin level was significantly lower at overweight ($p=0.001$) and obese patients ($p=0.001$) compared to controls (fig 1).

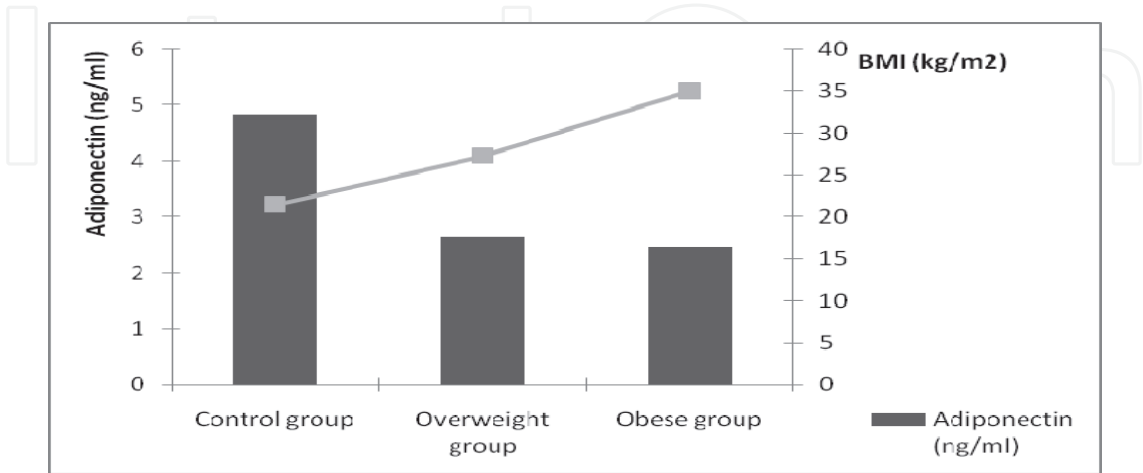


Fig. 1. Dynamics of adiponectin in correlation with the BMI of the studied patients

The nitrite level also decreased inversely correlated with the body mass index of the patients. Our data showing that the synthesis of NO at the endothelial level decreases from lean subjects to the overweight and obese ones might be also explained by the results of Chen et al (2003), which proved that adiponectin stimulates the NO production at the endothelial level (fig 2).

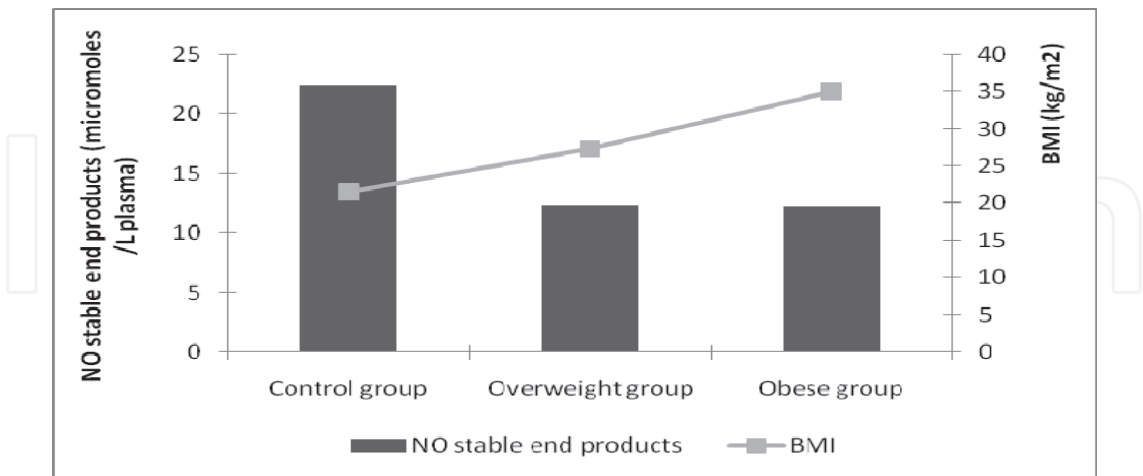


Fig. 2. The NO stable end products level in correlation with the BMI of the studied patients

For all the patients included in the study our results showed a significant, positive correlation between the adiponectin level and the NO stable end products (fig 3). This type of correlation also supports the theory that there is a regulatory mechanism between adiponectin and NO synthesis.

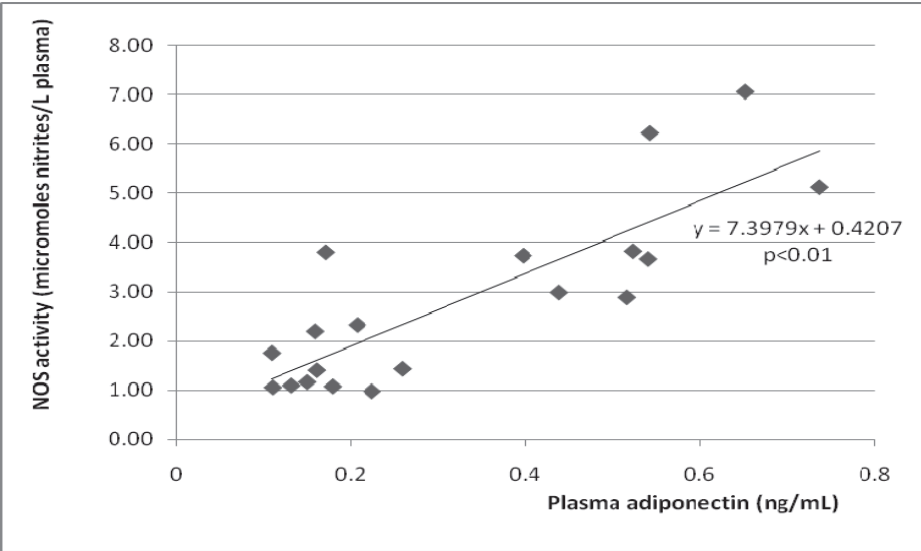


Fig. 3. The correlation between the NO stable end products and the plasma adiponectin level for the study group

The IL6 and hsCRP levels increased significantly at overweight and obese patients, in correlation with the BMI (fig 4). The increase was significant for the obese patients, in the case of both parameters and not significant for both parameters in overweight patients, compared to controls.

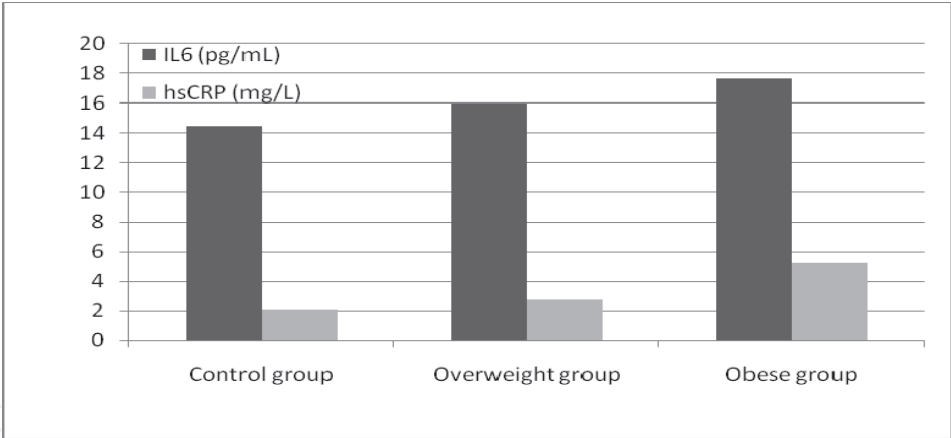


Fig. 4. IL6 and hsCRP levels for the studied groups

The E-selectin level was similar in the overweight and obese groups but was significantly higher ($p < 0.001$) compared to lean controls (fig 5). According to literature data, adhesion molecules of the selectin family are poorly expressed by the resting endothelium and are upregulated during atherogenesis, acute infections and granulomatous diseases. Thus, endothelial adhesion molecules are a result of both acute responses against pathogens and chronic inflammatory processes, such as those leading to progressive formation of atherosclerotic plaques (Ferri, 1998, Monaco, 2009). The elevated plasma levels of soluble endothelial adhesins might constitute indexes of increased adhesion molecule expression by the intact vascular endothelium in vivo. The results showing high levels of E-selectin in overweight and obese patients suggest that an early endothelial activation might be present in correlation with the weight increase, favoring the development of overt vascular lesions.

So, the vascular endothelium from obese patients releases endothelium-derived substances that can constitute markers of endothelial damage, such as E-selectin.

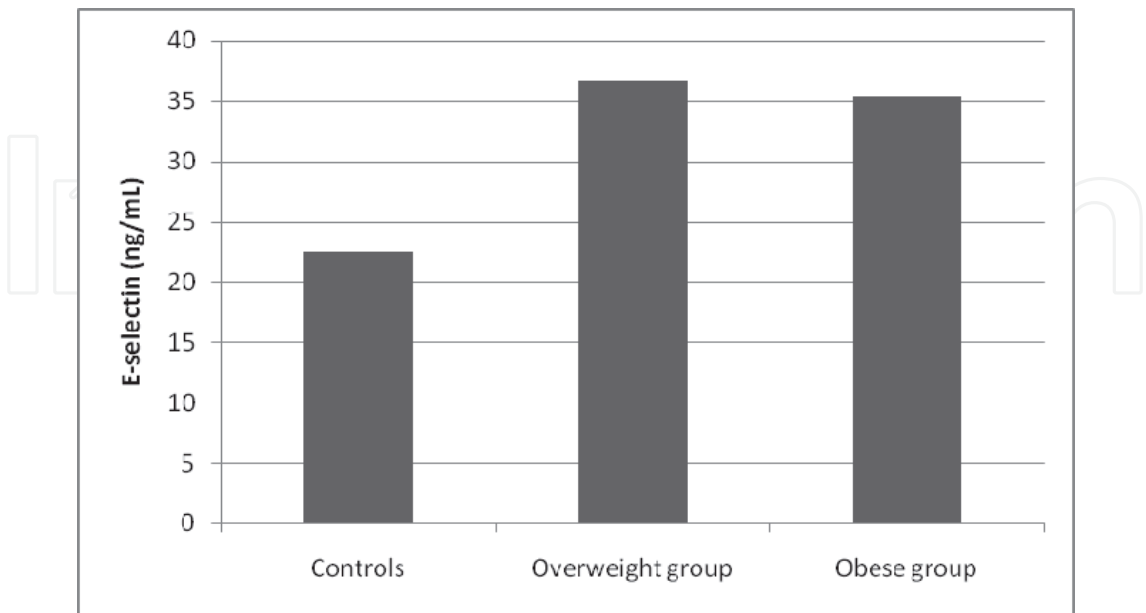


Fig. 5. E-selectin dynamics for the studied groups

The term “insulin resistance” as it is used in clinical and experimental settings refers to the inability of insulin to promote the normal homeostasis of glucose. That means that the reduced insulin action demands the presence of higher-than-normal concentrations of insulin in order to maintain a normal utilization of glucose by insulin target tissues. Thus, the term “insulin resistance” implies the existence of metabolic insulin resistance, which reflects an inadequate effect of insulin on glucose metabolism, but does not address other aspects of insulin action (Low Wang, 2004). Many investigators have studied simple surrogate indices of insulin resistance in comparison with the index assessed by euglycemic-hyperinsulinemic clamp. It has been established that homeostasis model assessment of insulin resistance HOMA-IR is a useful index of insulin resistance in diabetic and nondiabetic subjects and that its logarithmic transformation or its reciprocal value might make it more accurate (Mather et al, 2001, Yokoyama et al, 2003).

The HOMA model allows the evaluation of an insulin resistance index (HOMA-IR) and also of an index for the β -cell function (HOMA-B). These two parameters estimate the deficiency of the pancreatic β -cells based on a mathematical model that takes into account the interrelation (by negative feed-back) between glucose and insulin under normal metabolic control. This interrelation involves both the secretion of the pancreatic hormone and the hypoglycemic insulin action on target tissues. According to this model, the relationship between glucose and insulin, in the basal state, reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β -cells (Wallace, 2004, Rutter, 2008). Quicki is also defined as a result of the *in vivo* interaction between glucose and insulin in fasting conditions and, according to some investigators, reflects even better than HOMA, the variations of the insulin sensitivity of target tissues.

The literature data does not define reference values for HOMA and for Quicki parameters; clinical studies show that Quicki and 1/HOMA-IR are significantly lower in obese people compared to healthy subjects (Mather et al, 2001, Yokoyama et al, 2003). For the studied

patients we evaluated HOMA-IR and HOMA-B, the reciprocal value of HOMA-IR and Quicki (fig 6 and 7).

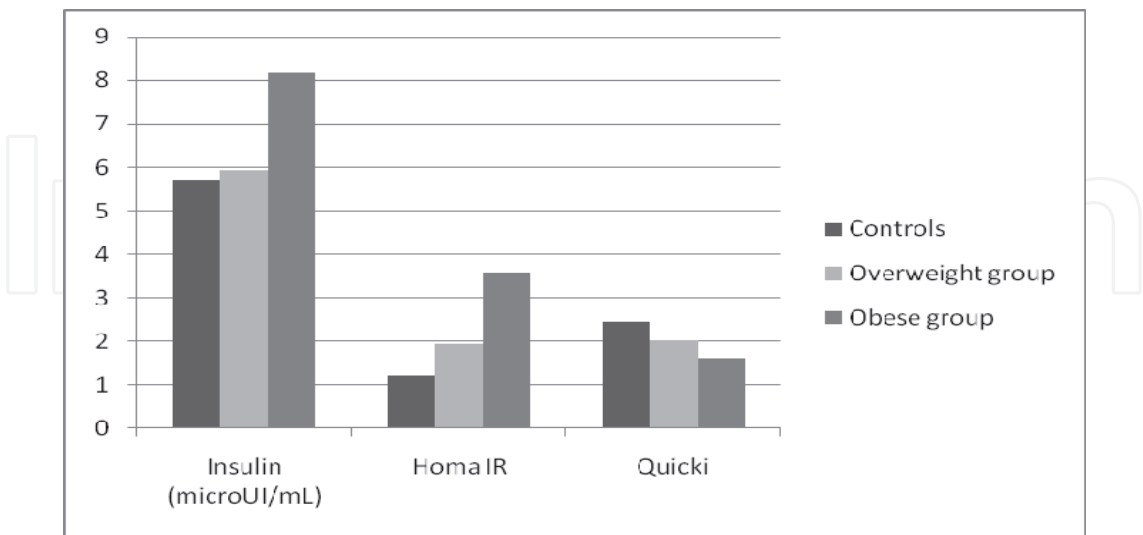


Fig. 6. The insulin as well as HOMA-IR and Quicki parameters for the studied groups

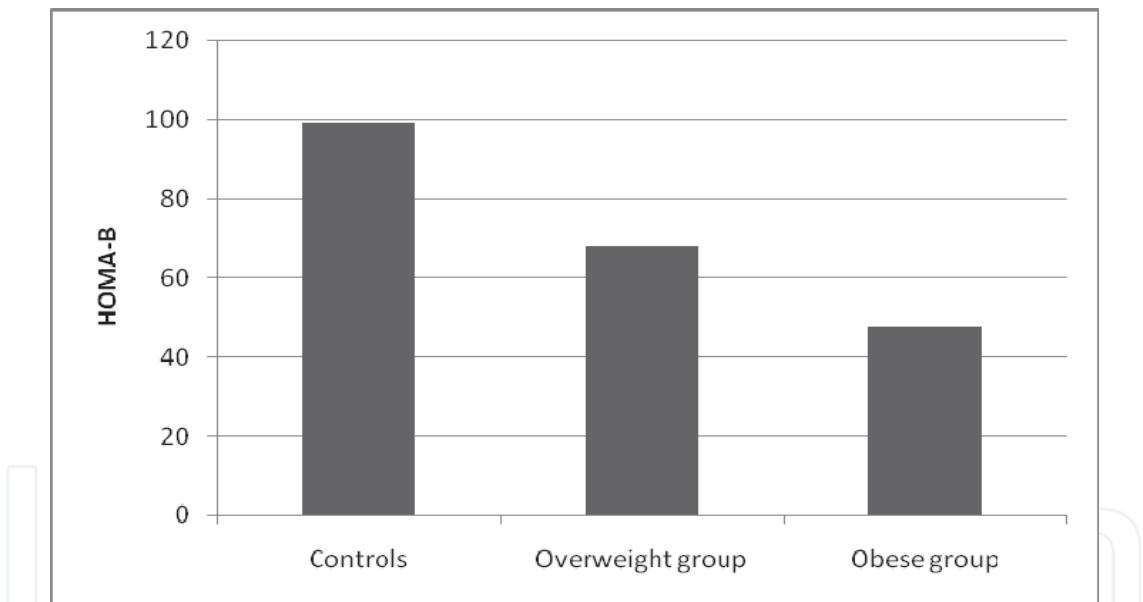


Fig. 7. The HOMA-B parameter for the three study groups

The increase of the insulin level is significant for the obese patients compared to controls. HOMA-IR and Quicki varied significantly in both overweight and obese subjects compared to controls. The insulin level and the insulin resistance index HOMA-IR increase from the control group to the overweight and significantly to the obese patients. So, in obese patients a significantly higher amount of insulin is necessary in order to maintain the normal fasting plasma glucose level; the weight increase might prevent the insulin, even if it's secreted in higher quantity, from exerting its action at the target tissues' level. In table 2 we present the values obtained for the reciprocal values and the logarithmic values of HOMA-IR, respectively.

Evaluated parameters	Control group	Overweight group	Obese group
Insulin (μUI/mL)	5.73±1.23	5.93±1.65	8.17±4.51**
1/HOMA-IR	0.86±0.17	0.68±0.28*	0.50±0.34**
Log(HOMA-IR)	0.103±0.07	0.24±0.22*	0.46±0.33**

Table 2. The values for 1/HOMA-IR and log (HOMA-IR) for the studied patients

The test used for the evaluation of the insulin resistance/sensitivity phenomena are significantly different both for overweight and obese patients compared to controls. Only the fasting level of insulin does not indicate the degree of insulin resistance. So, the calculated parameters show more precisely than the insulin evaluation the risk of secondary health issues associated with the body mass increase. These changes are revealed starting from the overweight stage and not from the obese stage, as it is the case with insulin. All the indexes used for the evaluation of insulin resistance/ β -cell function are significantly different for both overweight and obese patients compared to controls. For the studied patients, the decrease of the adiponectin level was correlated with an increase of HOMA-IR. The IL6 and hsCRP levels increased significantly in correlation with HOMA-IR (fig 8).

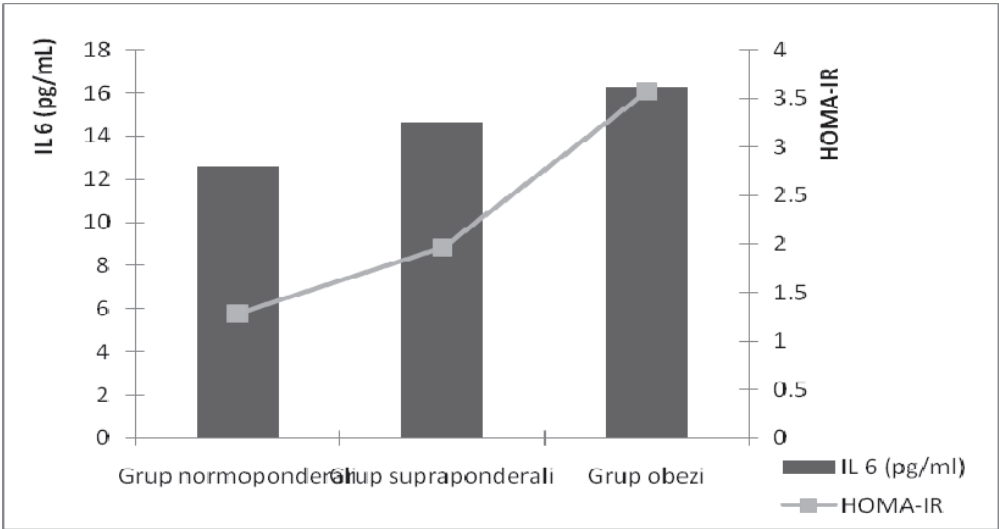


Fig. 8. Correlation of the IL6 level with HOMA-IR

IL6 production is increased in human obesity and the increase is correlated with an increase of the insulin resistance. IL6 can serve as a direct link between adipose tissue and insulin resistance. The American Diabetes Association defines pre-diabetes by levels of fasting plasma glucose (FPG) between 100 and 125 mg/dL. Analyzing the dynamics of insulin resistance parameters in the group of selected patients in correlation with the fasting plasma glucose level, we obtained the values presented in table 3. The analysis of the data depending both on the BMI and the fasting plasma glucose, shows that all of the parameters defined for the evaluation of insulin resistance and beta cell function increase significantly in the groups with FPG>125mg/dL, independently of their BMI. The control group and the overweight and obese groups with FPG<100mg/dL had similar values of the evaluated parameters (fig 9).

Evaluated parameters	Overweight group		Obese group	
	FPG<100mg/dL	FPG>125mg/dL	FPG<100mg/dL	FPG>125mg/dL
Insulin (μUI/mL)	5.68±0.81	6.72±2.79	5.53±1.30	10.22±5.29
HOMA-IR	1.22±0.21	3.55±1.63	1.26±0.35	5.58±2.78
1/HOMA-IR	0.85±0.17	0.35±0.18	0.84±0.20	0.22±0.10
Log(HOMA-IR)	0.11±0.05	0.51±0.22	0.12±0.09	0.70±0.21
HOMA-B	96.64±36.39	19.99±13.17	70.51±19.01	25.04±17.92
Quicki	2.42±0.57	1.24±0.36	2.41±0.65	0.99±0.20

Table 3. Parameters for the evaluation of beta cell function and insulin resistance in correlation with the fasting plasma glucose level

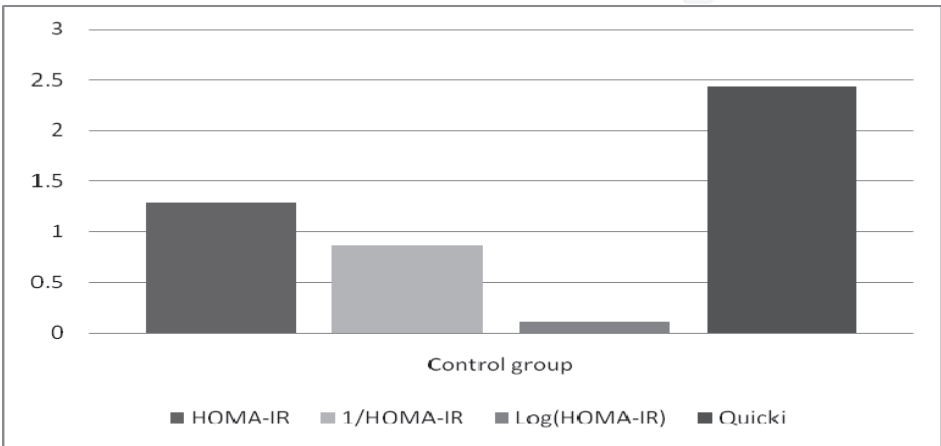


Fig. 9. Parameters for the evaluation of insulin resistance/sensitivity for the control group

The groups with FPG>125mg/dL, either overweight or obese showed significant increases of the parameters for the evaluation of insulin resistance or beta cell function compared to the control group.

The same kind of dynamics was obtained for the IL6 levels, which increased in both overweight and obese groups with FPG>125mg/dL, compared to the FPG<110mg/dl corresponding sub-groups (fig 10). The differences were significant only for the obese subgroups, and not-significant for the overweight ones, compared to controls.

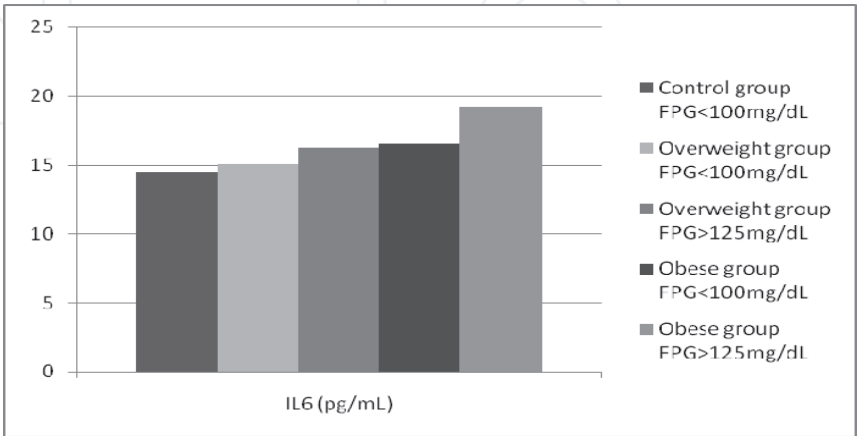


Fig. 10. Interlukin 6 dynamics in the subgroups of patients, defined both according to their BMI and their fasting plasma glucose level

No significant differences were recorded between the sub-groups, regarding the E-selectin levels (fig 11).

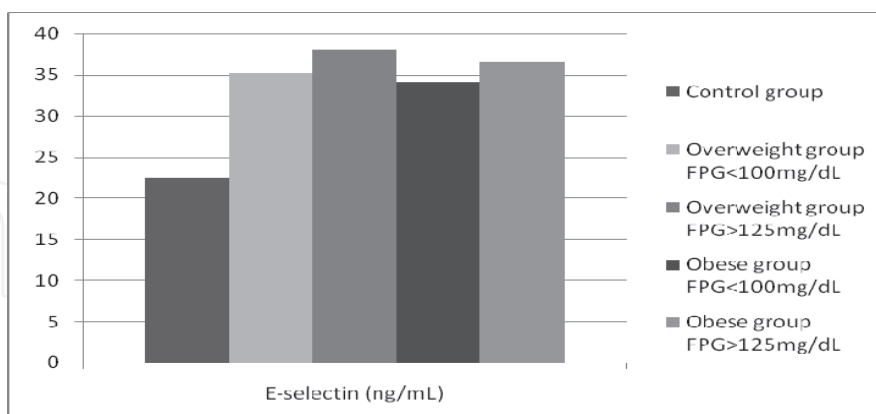


Fig. 11. E-selectin level for the sub-groups of patients, defined according both to their BMI and FPG

4. Conclusions

Our data revealed an impairment of the endothelial function expressed by both the decrease of the NO stable end products' and the adiponectin level, in the overweight and obese groups. These results are in agreement with data from Chen et al (2003), which proved that adiponectin stimulates the NO production at the endothelial level. The synthesis of IL6 as well as the hsCRP plasma level was highly correlated with the body mass index, suggesting the involvement of inflammatory phenomena in the development of endothelial dysfunction associated with the weight gain and the insulin resistance. So, the evaluation of adiponectin as well as of the NOS activity might prove to be useful predictive markers of atherogenic disorders at overweight and obese patients. Interleukin 6 is one of the molecules that contribute to the amplifying of the inflammatory signal in patients with dismetabolic syndrome, taking part into the relationship between the adipose tissue, the liver and the endothelium.

The current study demonstrates elevated plasma soluble adhesion molecule levels in weight increase patients with increased insulin resistance indexes, in spite of the absence of overt vascular damage. On the other hand, the increase of the E-selectin level, associated with the decrease synthesis of NO shows an activation of the endothelium, associated with the insulin resistance. We hypothesized that the early endothelial activation precedes the onset of overt vascular damage in obese patients and might be responsible for the increased release of E-selectin into the bloodstream.

Since insulin resistance is frequently associated as predictor or pathogenic factor in different pathological conditions (type 2 diabetes mellitus, obesity, glucose intolerance, essential hypertension, polycystic ovary syndrome), it is important to have simple, accessible tools for the evaluation of insulin sensitivity of target tissues to the insulin action in humans. The euglycemic hyperinsulinemic clamp technique remains the reference method for quantifying the sensitivity to insulin action but it cannot be applied on a large scale or in the context of routine investigations. For this reason, alternative methods have been developed, including the HOMA model and the Quicki test.

Our results show that the above mentioned parameters vary significantly in correlation with both weight and glucose level in a group of Romanian subjects.

The parameters for the evaluation of insulin resistance and beta cell function might be used in clinical studies in correlation with the level of fasting plasma glucose and not simply as indicators of the degree of insulin resistance in overweight and obese patients.

Since inflammation is an important feature of hyperglycemia and insulin resistance, future therapy for these pathological conditions should focus not only on the reduction of the plasma glucose and/or the glycated hemoglobin levels but also on the decrease of the inflammatory markers, in order to protect the endothelium and to reduce the associated cardio-vascular risk.

5. Acknowledgements

The work was performed under the CNCSIS/UEFISCDI grant PD 132/30.07.2010 (PD 29/2010).

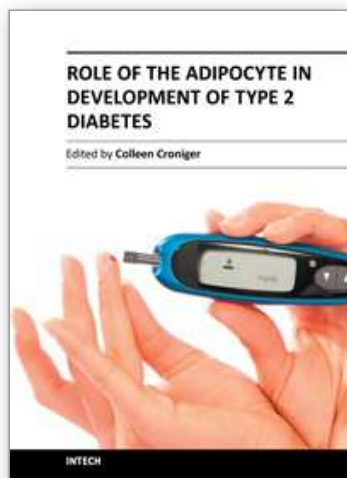
6. References

- Archer S. (1999) Measurement of nitric oxide in biological models, 2003, *The FASEB Journal*, Vol 7, No 2, 349-360, ISSN 1530-6860.
- Arita Y., Kihara S., Ouchi N., Takahashi M., Maeda K., Miyagawa J., Hotta K., Shimomura I., Nakamura T., Miyaoka K., Kuriyama H., Nishida M., Yamashita S., Okubo K., Matsubara K., Muraguchi M., Ohmoto Y., Funahashi Y. & Matsuzawa Y. (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem. Biophys. Res. Commun.* Vol 257, No 1, 79-83, ISSN 0006-291X.
- Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications, *Nature*, Vol 414, No 6865, 813-820, 0028-0836.
- Ceriello A., Quagliaro L., Piconi L., Assaloni R., Da Ros R., Maier A., Esposito K. & Giugliano D. (2004) Hyperglycemia on Circulating Adhesion Molecules and Oxidative Stress Generation and the Possible Role of Simvastatin Treatment, *Diabetes*, Vol 53, 701-710, ISSN 0012-1797
- Chen, H., Montagnani M., Funahashi T., Shimomura I. & Quon M.J. (2003) Adiponectin stimulates production of nitric oxide in vascular endothelial cells, *J Biol Chem*, Vol 45, No 278, 45021-45026, ISSN 1083-351X.
- Dansuntornwong B., Chanprasertyothin S., Jongjaroenprasert W., Ngarmukos C., Bunnag P, Puavilai G. & Ongphiphadhanakul B. (2007) The Relation between Parameters from Homeostasis Model Assessment and Glycemic Control in Type 2 Diabetes, *J Med Assoc Thai*, Vol 11, No 90, 2284-2290, ISSN 0007-1323.
- De Fronzo R.A. (1988) The triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes*, Vol 37, 667-687, ISSN 0012-1797.
- De Fronzo RA & Ferrannini E. (1991) Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease, *Diabetes Care*, Vol 14, 173-194, ISSN: 0149-5992.
- de Luca C. & Olefsky J.M. (2008) Inflammation and insulin resistance, *FEBS Letters* Vol 1, No 582, 97-105, ISSN: 0014-5793.
- Ferri C., Desideri G., Baldoncini R., Bellini C., De Angelis C., Mazzocchi C. & Santucci A. (1998), Early Activation of Vascular Endothelium in Nonobese, Nondiabetic

- Essential Hypertensive Patients With Multiple Metabolic Abnormalities, *Diabetes* Vol 47, 660–667, ISSN 0012-1797.
- Foss-Freitas M.C. & Foss M.C. (2004) Comparison of the homeostasis model assessment and quantitative insulin sensitivity check index with data from forearm metabolic studies for the *in vivo* assessment of insulin sensitivity, *Brazilian Journal of Medical and Biological Research*, Vol 5, No 37, 663–668, ISSN 1678-4510.
- Garcia C. Feve B., Ferré P., Halimi S., Baizri H., Bordier L., Guiu G., Dupuy O., Bauduceau B. & Mayaudon H. (2010) Diabetes and inflammation: Fundamental aspects and clinical implications, *Diabetes & Metabolism*, Vol 5, No 36, 327–338, ISSN: 1262-3636.
- Goldstein, B.J. & Scalia R. (2004) Adiponectin: a novel adipokine linking adipocytes and vascular function. *J. Clin. Endocrinol. Metab.* Vol 6, No 89, 2563–2568, ISSN: 1945-7197.
- Gradinaru D., Margina D. & Mitrea N., Study Concerning the Influence of Antianginal Therapy on the Activity of Endothelial Nitric Oxide Synthase, *Farmacia*, Vol 45, Nr. 3, 2003, 42-51, ISSN: 0014-8237.
- Guizea L., Panniera B., Thomasa F., Beana K., Jégoa B. & Benetos A. (2008) Recent advances in metabolic syndrome and cardiovascular disease, *Archives of Cardiovascular Disease*, Vol 9, No 101, 577–583, ISSN: 1875-2136.
- Hansson G.K. (2005) Inflammation, Atherosclerosis and Coronary Artery Disease, *New England Journal of Medicine*, Vol 16, No 352, 1685-1695, ISSN 1533-4406.
- Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S. & Hanafusa T, Matsuzawa (2000) Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler. Thromb. Vasc. Biol.*, Vol 6, No 20, 1595–1599, ISSN: 1079-5642.
- Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, Fu Y, Motone M, Yamamoto K, Matsuo A, Ohashi K, Kihara S, Funahashi T, Rakugi H, Matsuzawa Y. & Ogihara T. (2004) Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension*. Vol 6, No 43, 1318–1323, ISSN: 02636352.
- Joussen AM, Poulaki V, Qin W, Kirchhof B, Mitiades N, Wiegand SJ, Rudge J, Yancopoulos GD. & Adamis AP (2002) Retinal vascular endothelial growth factor induces intercellular adhesion molecule-1 and endothelial nitric oxide synthase expression and initiates early diabetic retinal leukocyte adhesion in vivo. *Am J Pathol* Vol 2, No 160, 501–509, ISSN 0002-9440.
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G. & Quon MJ (2000) Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*, Vol 7, No 85, 2402–2410, ISSN 1945-7197.
- King GL, Kunisaki M, Nishio Y, Inoguchi T, Shiba T. & Xia P (1996) Biochemical and molecular mechanisms in the development of diabetic vascular complications. *Diabetes* Vol 45 (Suppl. 3), S105–S108, ISSN 0012-1797.
- Low Wang C.C., Goalstone M.L. & Draznin B. (2004) Molecular Mechanisms of Insulin Resistance That Impact Cardiovascular Biology, *Diabetes* Vol 11, No 53, 2735–2740, ISSN 0012-1797.

- Margină D, Vlădică M, Grădinaru D, Mitrea N, Dănciulescu R & Radulian G (2005) Clinical study regarding the relationship between the interleukin 6 level, insulin resistance and endothelial dysfunction, *Farmacia*, No 6, 18-24, ISSN: 0014-8237.
- Mather KJ, Hunt AE, Steinberg HO, Paradisi G, Hook G, Katz A, Quon MJ. & Baron AD (2001) Repeatability characteristics of simple indices of insulin resistance: implications for research applications. *J Clin Endocrinol Metab*, Vol 11, No 86, 5457-5464, ISSN 1945-7197.
- Matsuda M. (2010) Measuring and estimating insulin resistance in clinical and research settings, *Nutrition, Metabolism & Cardiovascular Diseases* Vol 2, No 20, 79-86, ISSN: 0939-4753.
- McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA. & Duncan AW (2001) Diagnosing insulin resistance in the general population, *Diabetes Care*, Vol 3, No 24, 460-464, ISSN: 0149-5992.
- Miyamoto K, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, Aiello LP, Ogura Y. & Adamis AP (1999) Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition, *Proc Natl Acad Sci U S A*, Vol 19, No 96, 10836 -10841, ISSN 0027-8424.
- Monaco C., Gregan S.M., Navin T.J., Foxwell B.M.J., Davies A.H. & Feldmann M (2009) Toll-Like Receptor-2 Mediates Inflammation and Matrix Degradation in Human Atherosclerosis, *Circulation.*, Vol 24, No 120, 2462-2469, ISSN: 0009-7322.
- Moshage H., Kok B., Huizenga J.R. & Jansen P.L.M. (1995) Nitrite and nitrate determination in plasma: a critical evaluation, *Clin. Chem.*, Vol 6, No 41, 892-896, ISSN 0009-9147.
- Ouchi N., Kihara S., Arita Y., Okamoto Y., Maeda K., Kuriyama H., Hotta K., Nishida M., Takahashi M., Muraguchi M., Ohmoto Y., Nakamura T., Yamashita S., Funahashi T. & Matsuzawa Y. (2000) Adiponectin, an adipocyte derived plasma protein, inhibits endothelial NFkappaB signaling through a cAMP-dependent pathway. *Circulation*, Vol 11, No 102, 1296-1301, ISSN: 0009-7322.
- Ouedraogo R., Gong Y., Berzins B., Wu X., Mahadev K., Hough K., Chan L., Goldstein B.J., & Scalia R. (2007) Adiponectin deficiency increases leukocyte-endothelium interactions via upregulation of endothelial cell adhesion molecules in vivo, *J. Clin. Invest.*, Vol 6, No 117, 1718-1726, ISSN: 0021-9738.
- Ray A., Huisman M.V., Tamsma J.T.; van Asten J., Bingen B.O., Broeders E.A., Hoogeveen E.S., van Hout F., Kwee V.A., Laman B., Malgo F., Mohammadi M., Nijenhuis M., Rijkée M., van Tellingen M.M., Tromp M., Tummers Q. & de Vries L. (2009) The role of inflammation on atherosclerosis, intermediate and clinical cardiovascular endpoints in type 2 diabetes mellitus, *European Journal of Internal Medicine* Vol 3, No 20, 253-260, ISSN: 0953-6205.
- Rutter M.K., Wilson P.W.F, Sullivan L.M., Fox C.S., D'Agostino R.B. & Meigs J.B. (2008) Use of Alternative Thresholds Defining Insulin Resistance to Predict Incident Type 2 Diabetes Mellitus and Cardiovascular Disease, *Circulation.*, Vol 8, No 117, 1003-1009, ISSN: 0009-7322.
- Scherer, P.E. (2006) Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes*. Vol 6, No 55, 1537-1545, ISSN 0012-1797.
- Song Y., Manson J.E., Tinker L., Howard B.V., Kuller L.H., Nathan L., Rifai N. & Liu S. (2007) Insulin Sensitivity and Insulin Secretion Determined by the Homeostasis Model Assessment (HOMA) and Risk of Diabetes Mellitus in a Multi-Ethnic Cohort

- of Women: The Women's Health Initiative Observational Study, *Diabetes Care*, Vol 7, No 30, 1747-52, ISSN: 0149-5992.
- Soonthornpun S., Setasuban W., Thamprasit A., Chayanunnukul W., Rattarasarn C. & Geater A. (2003) Novel Insulin Sensitivity Index Derived from Oral Glucose Tolerance Test, *The Journal of Clinical Endocrinology & Metabolism*, Vol 3, No 88 1019-1023, ISSN: 1945-7197.
- Stühlinger M.C., Abbasi F., Chu J.W., Lamendola C., McLaughlin T.L., Cooke J.P., Reaven G.M. & Tsao P.S. (2002) Relationship Between Insulin Resistance and an Endogenous Nitric Oxide Synthase Inhibitor, *JAMA*, Vol 11, No 287, 1420-1426, ISSN 0002-9955.
- Wallace T.M., Levy J.C. & Matthews D.R. (2004) Use and Abuse of HOMA Modeling, *Diabetes Care*, Vol 6, No 27, 1487-1495, ISSN: 0149-5992.
- Tataranni P.A. & Ortega E. (2005) A Burning Question. Does an Adipokine-Induced Activation of the Immune System Mediate the Effect of Overnutrition on Type 2 Diabetes?, *Diabetes*, Vol 4, No 54, 917-927, ISSN 0012-1797.
- Veves A, Akbari CM, Primavera J, Donaghue VM, Zacharoulis D, Chrzan JS, DeGirolami U, LoGerfo FW & Freeman R (1998) Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration. *Diabetes*, Vol 3, No 47, 457- 463, ISSN 0012-1797.
- Wadham C., Parker A., Wang L. & XiaP. (2007) High Glucose Attenuates Protein S-Nitrosylation in Endothelial Cells. Role of Oxidative Stress, *Diabetes*, Vol 11, No 56, 2715-2721, , ISSN 0012-1797.
- Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC & Creager MA: (1998) Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation* 97:1695-1701, ISSN: 0009-7322.
- Yokoyama H., Emoto M., Fujiwara S., Motoyama K., Morioka T., Komatsu M., Tahara H., Shoji T., Okuno Y. & Nishizawa Y. (2003) Quantitative Insulin Sensitivity Check Index and the Reciprocal Index of Homeostasis Model Assessment in Normal Range Weight and Moderately Obese Type 2 Diabetic Patients, *Diabetes Care*, Vol 8, No 26, 2426-2432, ISSN: 0149-5992.
- Zavaroni I, Piatti PM, Monti LD, Gasparini P, Barilli LA, Massironi P, Ardigo D, Valsecchi G, Delsignore R & Raven GM (2000): Plasma nitric oxide concentrations are elevated in insulin resistant healthy subjects. *Metabolism*, Vol 8, No 49, 959-961, ISSN: 0026-0495.



Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

ISBN 978-953-307-598-3

Hard cover, 372 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Denisa Margina (2011). Inflammatory Markers Associated with Chronic Hyperglycemia and Insulin Resistance, Role of the Adipocyte in Development of Type 2 Diabetes, Dr. Colleen Croniger (Ed.), ISBN: 978-953-307-598-3, InTech, Available from: <http://www.intechopen.com/books/role-of-the-adipocyte-in-development-of-type-2-diabetes/inflammatory-markers-associated-with-chronic-hyperglycemia-and-insulin-resistance>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen