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Plasma Concentration of Adipokines, Obstructive Sleep Apnea Syndrome and Chronic Kidney Disease in Patients with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease

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1. Introduction

It is widely accepted that manifestation of target organs damage in patients with metabolic syndrome (MS) often has simultaneous and rapid pattern. Non-alcoholic fatty liver disease (NAFLD) has been described as one of metabolic syndrome-induced target organ damage. NAFLD clinical manifestations vary from ultrasonographically detected liver steatosis to non-alcoholic steatohepatitis (NASH) (Sowers, 2008). Detailed analysis of NAFLD relationship with other organs impairment in MS patients is particularly important for diagnostic procedures adjustment and optimization of treatment.

Different experimental and clinical research data demonstrate strict relation between NAFLD and chronic kidney disease (CKD). In a population study including more than 8,000 healthy men, recruited in South Korea, NAFLD with elevated serum gamma-glutamyltransferase (GGT) concentration was associated with an increased CKD risk among nondiabetic, nonhypertensive men, irrespective of metabolic syndrome. The association was evident even after adjustment for age, glomerular filtration rate (GFR), triglycerides, and high-density lipoprotein cholesterol (Chang et al., 2008). Another study data suggested that NAFLD is associated with an increased prevalence of CKD in type 2 diabetic individuals independent from numerous baseline confounding factors (Targher et al., 2008).

Presence of association between NAFLD and CKD revealed similar risk factors and rate of their coexistence in MS patients and could be explained by similar development mechanisms. Multiple mediators known as adipokines expressed are secreted by adipocytes and play an important role in the induction of endothelial dysfunction, tissue hypertrophy and fibrosis even at an early stage of target organ damage (Antuna-Puente et al., 2008). Pair

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of adipokines – leptin and adiponectin are physiological antagonists. Combination of leptin hyperproduction and peripheral tissues resistance to it in patients with abdominal type of obesity is paired with protector insufficiency – adiponectin. It leads to progression of dysmetabolism, particularly insulin resistance development and organ remodeling intensification (Anubhuti & Arora, 2008; Han et al., 2009). Obstructive sleep apnea syndrome (OSAS) could be integral pathogenetic chain in CKD and NAFLD (Tokuda et al., 2008). Investigation of correlation between plasma leptin and adiponectin concentrations, OSAS and CKD development in NAFLD patients gives opportunity to get closer to mechanisms of target organs damage in MS with subsequent optimization of prophylactic strategy.

2. Materials and methods

Research involved 86 patients (64 males and 22 females) with MS diagnosed according to standard criteria (Alberti et al., 2006) and NAFLD (ultrasonic proven liver steatosis in combination with elevated transaminases, GGT and/or alkaline phosphatase level increase without signs of viral hepatitis or other diseases with hepatic manifestation).

All the patients had abdominal obesity (waist circumference (WC) >94 cm in males and >80 cm in females (Alberti et al., 2006)). Mean age was 44.0 ± 11.0 .

Along with general investigation all patients were tested for common risk factors presence and severity (Mancia et al., 2009). Blood pressure was measured using a standard mercury sphygmomanometer under standard conditions as mentioned in cardiovascular survey methods. Each person was examined for height, weight and WC without shoes with minimal clothing as per cardiovascular survey methods. Body mass index (BMI) was calculated by formula of weight in kg/height m². All patients underwent biochemical tests: concentrations of HDL cholesterol, LDL cholesterol, VLDL cholesterol, total cholesterol and triglycerides (Biosystems S.A. kit, Spain) were measured on automatic analyzer Beckman Synchron Clinical System CX5delta; also atherogenic index was calculated using equation: atherogenic index = (total cholesterol – HDL cholesterol) / HDL cholesterol.

Presence and grade of insulin resistance and disturbances of carbohydrates metabolism related to it were estimated by fasting serum glucose level (Biosystems S.A. kit, Spain), C-peptide (DPC kit, USA), fasting insulin serum concentration (DPC kit, USA) and HOMA-index calculation (fasting glucose (mmol/L) x insulin (IU/mL) / 22.5).

Plasma concentration of adipokines – leptin and adiponectin were measured by immune-enzyme analysis (“Human Adiponectin ELISA” (BioVendor GmbH, Germany), “Leptin (Sandwich) Elisa” (DRG, USA)).

Signs of target organs damage were registered according to standard recommendations (Alberti et al., 2006): left ventricular hypertrophy was diagnosed echocardiographically using Sokolow-Lyon criteria and left ventricular mass index (Acuson Sequoia 512 (Siemens Acuson, USA)); atherosclerotic involvement of carotid artery was diagnosed by ultrasonic investigation of carotid artery intima-media thickness (CIMT) and/or by detection of atherosclerotic plaque in its wall (ESAOTE (Technos MPX, Italy)); albuminuria was estimated using nephelometric assay (Image Immunochemistry Systems, Beckman Coulter, USA), GFR was estimated using MDRD formula.

For statistical processing data were analysed by STATISTICA 8.0 (StatSoft, Russia). Various numbers are given as mean value and standard deviation (for normal distribution); median value and interquartile range (for asymmetric distribution). Categorical variables have been

compared by parametric and nonparametric methods. The Pvalue < 0.05 was considered as significant.

3. Results

Patients were divided into two groups depending on stage of NAFLD: 48 subjects with clinically unsuspected liver steatosis detected only by ultrasonic investigation and 38 subjects with signs of NASH. Transaminases and G-GT serum levels were comparatively higher in patients with NASH (Table 1), whereas De Ritis ratio was comparatively higher in patients with liver steatosis.

	NASH(n=38)	Liver steatosis (n=48)
AST, IU/mL	54±31*	24±8
ALT, UI/mL	99±73*	32±17
De Ritis ratio	0.6±0.2*	0.8±0.2
G-GT, IU/mL	97±65*	47±30

Table 1. Serum AST, ALT, G-GT levels and De Ritis ratio in patients with MS and NAFLD (n=86). * P<0.001

Comparison of CKD and NASH prevalence rate according to number of damaged target organs revealed that both CKD and NASH prevalence was significantly higher in group of patients with ≥3 target organ damage (Table 2) and lower in other groups (patients with 1 or 2 target organ damage). The patients with 2 and ≥3 target organ damage showed significant increase in albuminuria level. There was no significant difference in plasma concentrations of adiponectin and leptin in all the groups, but ratio leptinemia/adiponectinemia increased significantly in concordance with number of damaged target organ and reached maximum in patients with ≥3 target organ damage.

	1 target organ damage (n=18)	2 target organ damage (n=39)	≥3 target organ damage (n=18)
CKD rate, %	17% P<0.05 vs 2 и ≥3	44%	67%
NASH rate, %	39% P<0.05 vs ≥3	44%	78% P<0.05 vs 2
Albumiuria, mg/24h	6.0 (4.3 – 9.0) P<0.05 vs 2 and ≥3	12.6 (8.0 – 38.0)	30.2 (17.3 – 48.0)
Leptin, ng/mL	23.6±23.4	31.6±27.3	31.2±26.0
Adiponectin, µg/mL	31.3±17.5	22.9±20.2	11.8±5.5
Leptin/ Adiponectin	1.0±0.8 P<0.05 vs 2 and ≥3	1.7±1.4	3.1±1.6 P<0.05 vs 2

Table 2. CKD and NASH prevalence, albuminuria and adipokines plasma concentration in patients with MS and NAFLD (n=86).

Among all patients with MS and NASH 37.2% (32 patients) were diagnosed CKD, 26 of them had microalbuminuria, 6 subjects had urinary albumin excretion over 300 mg/24h. Five patients had CKD III stage (GFR <60 mL/min/1.73m²), all of them also had signs of NASH. Patients with MS, NAFLD and CKD showed marked insulin resistance: fasting insulinemia level, HOMA index and plasma C-peptide concentration in this type of patients were higher than in patients with NAFLD without CKD (Table 3). Moreover in patients with MS, NAFLD and CKD registered significantly higher plasma leptin level.

	Patients with CKD (n=32)	Patients without CKD (n=54)
Insulin, μU/mL	16.8±9.2	11.5±5.6**
HOMA index	4.2±2.2	2.9±1.5**
C-peptide, pmol/L	1326±411	999±341***
Leptin, ng/mL	38.2±28.8	21.6±19.8*
Adiponectin, μg/mL	23.7±19.5	18.1±14.8
Leptin/Adiponectin	2.15±1.58	1.71±1.52

Table 3. Comparison of insulin resistance and plasma adipokines levels in patients with MS and NAFLD in case of CKD presence or absence. *-P=0.003; **-P=0.002; ***-P<0.001.

Correlation analysis showed direct correlation of leptin concentration and BMI, systolic blood pressure, adiponectin level and albumiuria (Table 4). Adiponectin level correlated directly with leptin level, serum HDL cholesterol concentration and De Ritis ratio. Inverse correlation was registered between atherogenic index, CIMT and serum level of adiponectin.

Parameter	Leptin	Adiponectin
BMI	r = 0.27*	r = 0.29
WC	r = 0.21	r = 0.33
Systolic blood pressure	r = 0.24*	r = 0.10
Atherogenic index	r = -0.14	r = -0.43*
HDL cholesterol	r = 0.18	r = 0.43*
CIMT	r = -0.04	r = -0.38*
HOMA index	r = 0.32*	r = -0.18
C-peptide	r = 0.29*	r = -0.02
Insulin	r = 0.35*	r = -0.10
De Ritis ratio	r = 0.13	r = 0.36*
Leptin	-	r = 0.39*
Adiponectin	r = 0.39*	-
Albuminuria	r = 0.28*	r = 0.19

Table 4. Correlation of plasma adipokines concentration with MS criteria and target organs damage in patients with MS and NAFLD (n=86). * - significant correlations

OSAS was diagnosed in 20 (24%) patients (Table 5). These patients had significantly higher blood pressure, BMI, WC, fasting insulin serum concentration and C-peptide. Obese patients with OSAS demonstrated significantly marked target organs damage signs (higher

level of albuminuria and lower GFR) in comparison with obese patients without OSAS. Also obese patients with CKD developed OSAS more frequent than obese patients without CKD (38% and 15% respectively, P=0.018).

Index	OSAS	
	Presence (n=20)	Absence (n=66)
Male/female	17/3	47/19
Mean age, years old	45±10	43±11
Mean blood pressure, mm/Hg	106±9	100±9
BMI, kg/m²	39.8±7.9**	31.5±4.3
WC, cm	125±17**	108±11
HOMA-index	4.1±1.9*	3.1±1.9
C-peptide, pmol/L	1337±422*	1092±384
Leptin, ng/mL	36.7±29.9	25.3±23.0
Adiponectin, µg/mL	20.4±10.8	21.2±19.1
Insulin, µU/mL	16.9±7.8*	12.7±7.3
Albuminuria, mg/24h	21.0 (12.0;38.4)*	10.3 (6.3;19.4)
GFR, mL/min/1.73m²	81±17*	95±24

Table 5. Clinical and laboratory characteristics of patients with MS and NAFLD (n=86) in case of OSAS presence or absence. *-P<0.05; **-P<0.001

4. Discussion

According to our data an increase of target organs damage in patients with MS and NAFLD leads to an increase of CKD and NASH development rate and albuminuria level. Relationship of NAFLD and albuminuria was also shown in other clinical invetigations. Hwang S.T. et al. examined 1361 patients with type 2 diabetes mellitus and prediabetes (Hwang et al., 2010). The patients with NAFLD had higher prevalence rates of microalbuminuria (6.3% vs 19%; P=0.001 in prediabetes, 4.5% vs 32.6%; P<0.001 in diabetes) and also had a greater albumin-to-creatinine ratio (14.6 +/- 52.0 µg/mg Cr vs 27.7 +/- 63.9 µg/mg Cr; P=0.051 in prediabetes, 11.4 +/- 21.4 µg/mg Cr vs 44.7 +/- 76.4 µg/mg Cr; P<0.001 in diabetes) than those without NAFLD. NAFLD was associated with 3.66 (P=0.013) times higher rate of microalbuminuria in prediabetes patients and 5.47 (P=0.048) times higher in diabetes patients. Our patients with MS and NAFLD showed highest albuminuria level in the group with highest NASH prevalence rate. Leptin/adiponectin ratio raised significantly in observed by our team patients with MS and NAFLD when albuminuria level and NASH prevalence rate increased. It probably indicates that increased expression of tissue-destructive adipokine – leptin is not combined with adequate plasma concentration increase of protective adipokine – adiponectin. It was shown that the increase of leptin/adiponectin ratio is associated with increase of visceral fat mass, MS prevalence (Kumagai et al., 2005) and severity of insulin resistance (Oda et al., 2008).

Both insufficient adiponectin effect and leptin hyperproduction predetermine the increase of insulin resistance. It reaches maximum level in the group of patients with NAFLD and CKD demonstrating highest values of fasting insulin serum concentration, C-peptide and HOMA-index. Evidently insulin resistance in such patients is caused mainly by leptin excess (Anubhuti & Arora, 2008), which maximal plasma concentration registered in patients with NAFLD and CKD. Leptin contribution to insulin resistance of peripheral tissues intensification is more evident as NAFLD progresses and CKD develops, adiponectin plasma concentration and its tissue protective effect gradually decrease (this is also evidenced by our observation of significant leptin/adiponectin ratio increase). It should be noted that leptin mainly shows properties similar to insulin excess and hereby comes into synergic effect with it, in particular by inducing expression of profibrogenic chemokines in target tissues (e.g. transforming growth factor beta (TGF- β)) leading to tissue fibrosis development. Currently, the role of leptin in kidney tissue fibrosis development is clear (Wolf & Ziyadeh, 2006), pathogenetic role of obesity as CKD risk factor in general population determined in several epidemiological investigations (Foster et al., 2008; Kramer et al., 2005) could be explained by consequences of hyperleptinemia (similar as adiponectin insufficiency). It was also shown that leptin directly increases fibrogenesis in liver tissue in patients with NAFLD. Ikejima K. et al. demonstrated leptin key role in stimulation of TGF- β mRNA expression in Kupffer cells and sinusoidal endothelial cells in rodents with genetically determined leptin and leptin receptor deficiency (Ikejima et al., 2005). Moreover, leptin augmented platelet derived growth factor-dependent proliferation of hepatic stellate cells by enhancing downstream intracellular signaling pathways. Hereby NAFLD and CKD progression in patients with MS is determined mainly by profibrogenic effect of leptin and excess of insulin.

Along with indicated above, leptin and insulin induced endothelial dysfunction could stand as another common mechanism of NAFLD and CKD development. Increasing albuminuria is a local kidney marker of endothelial dysfunction. It was proved, that hyperleptinemia directly related to microalbuminuria in patients with abdominal obesity (Ikee et al., 2008). Close associations of NAFLD with global impairment of endothelial function were estimated. Thus, examination of 250 obese children showed that presence of NAFLD entails more severe functional and anatomic changes in the arterial wall. Flow-mediated vasodilatation of brachial artery (one of the signs of endothelial dysfunction) was remarkably reduced and CIMT was increased in obese subjects with confirmed MS and NAFLD (Pacifico et al., 2010). Hypertensive patients with NAFLD have a reduced endothelium-dependent vasodilation and highest insulin resistance in comparison with hypertensive patients without NAFLD. In keeping with this, it is possible to hypothesize that liver steatosis may be considered a marker of vascular damage in essential hypertension (Sciacqua et al., 2010). Integrally, NAFLD presence in patients with MS is always combined with the most pronounced endothelial dysfunction, which mainly predetermines intensity of other target organs remodeling, including kidney. The role of hepatic endothelial cells impaired function, related to hyperleptinemia, insulin resistance and insufficient effects of adiponectin, in progression of NAFLD could not be completely excluded. Development of specific laboratory investigation methods is necessary to evaluate their contribution.

Relationships between NAFLD and CKD revealed in this research in patients with MS could be explained by an imbalanced action of antagonistic adipokines – leptin and adiponectin – and combined with it the intensification of insulin resistance. Taking into consideration our correlation analysis data leptin plasma concentration directly correlates with body mass; in

parallel with it – insulin resistance and albuminuria. In addition hyperleptinemia is associated with an increased blood pressure. Hypertensive effect of leptin was confirmed in general population. During one of the phases of prospective population investigation - Copenhagen City Heart Study - new-onset hypertension was examined in 620 women and 300 men who were normotensive in the previous examination, which was performed in 1991-1994 (Asferg et al., 2010). Leptin plasma concentration was significantly associated with new-onset hypertension (odds ratio of 1.28 (1.08-1.53; $P < 0.005$) for 1 s.d. higher level of log-transformed leptin), whereas adiponectin was not significantly associated with new-onset hypertension. Adiponectin plasma concentration directly correlated with concentration of HDL cholesterol, and correlated inversely with CIMT and atherogenic index. Our data matches generally accepted conception of adiponectin antiatherogenic properties and its ability to withstand intensification of metabolic disorders, particularly insulin resistance in patients with MS (Han et al., 2009).

Direct correlation between adiponectinemia and De Ritis ratio demonstrated in our study shows inhibitory action of adiponectin on NAFLD progression rate. In case of NASH onset in such patients adiponectin plasma concentration and level of its expression by liver tissue significantly decrease (Jiang et al., 2009; Ma et al., 2009). Thereby leptin/adiponectin imbalance may be regarded as one of the most important mechanisms of organ damage including CKD and NAFLD in patients with MS.

OSAS had a special place among other independent risk factors of CKD severity and progression in patients with MS and NAFLD examined by our team. Patients with OSAS showed maximum levels of insulin resistance markers and exactly those subjects demonstrated the highest albuminuria level and a lower level of estimated GFR in comparison with groups of patients with MS without OSAS. Recently OSAS has been considered as one of “most malignant” variant of MS, during which both target organ damage rate and severity of metabolic impairments could reach maximal intensity. Highest expression levels of adipokines with tissue-destructive effect, in particular – leptin were registered in patients with OSAS. Presence of direct significant correlation between leptin plasma concentration and apnea/hypopnea index was evaluated in patients with OSAS (Tokuda et al., 2008). Stepwise multiple regression analysis showed that BMI ($r=0.807$, $p<0.0001$), the percentage of time with less than 90% hemoglobin saturation level in total sleep time ($\%T<90$)($r=0.399$, $p<0.001$) and apnea/hypopnea index ($r=0.552$, $p<0.001$) were determinant factors for serum leptin levels. Thus, hyperleptinemia raised as OSAS severity and BMI increased. Among the patients who had successful surgical correction of OSAS (uvulopalatopharyngoplasty; or uvulopalatopharyngoplasty and tonsillectomy; or uvulopalatopharyngoplasty, tonsillectomy and radiofrequency ablation of the base of the tongue) leptin and other adipokines with similar effect (interleukin-6, tumor necrosis factor- α) plasma concentration dramatically decreased, whereas adiponectin plasma concentration significantly increased after surgery (Adeseun & Rosas, 2010).

Typical for OSAS adipokines hyperproduction leads to the enhancement of target organ damage development. It was confirmed in multiple clinical and epidemiological investigations. In this way OSAS is considered as one of CKD risk factors (Eun et al., 2010). Patients with OSAS demonstrate significantly lower estimated GFR in comparison with patients without OSAS (84.57 and 94.67 mL/min/1.73m² respectively, $P=0.037$) (Fleischmann et al., 2010). Patients with estimated GFR <60 mL/min/1.73m² show 6 times higher frequency of central apnea episodes in comparison with group of patients with estimated GFR >60 mL/min/1.73m². Presence of OSAS as concomitant condition in our

patients with NAFLD was associated with significant decrease of estimated GFR which was calculated using MDRD formula. Thereby this category of patients should be subjected to medical examination at first visit for detection of early stages of CKD (assessment of albuminuria level, estimated GFR, including new markers for GFR estimation, particularly cystatin C).

5. Conclusion

The results of our study indicate that in patients with MS a relationship exists between NAFLD and CKD: NASH development is closely related to increase in albuminuria levels. Association of NAFLD and CKD in patients with MS may be explained by mutual mechanisms of onset and progression, among which should be mentioned hyperleptinemia, lack of adiponectin effects and related to it increase of insulin resistance. From this point of view all the patients with MS and NAFLD must be checked for CKD signs (albuminuria, serum creatinine, estimated GFR). Dynamical changes of these markers could play the role of efficacy indicators of integral therapeutic approaches, e.g. medications for treatment of obesity (orlistat), oral hypoglycemic agents (metformin), antihyperlipidemic agents (statins, fenofibrate) and also several antihypertensive drugs (angiotensin receptor blockers).

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Clinical nephrology is an evolving speciality in which the amount of information is growing daily. This book gives quick access to some important clinical conditions encountered in nephrology including the diseases of glomeruli, tubules and interstitium. It presents the latest information on pathophysiology, diagnosis and management of important diseases of renal parenchyma. The information is presented in a very user friendly and accessible manner while the treatment algorithms enable the reader to quickly access expert advice on arriving at the most appropriate treatment regimen. The book discusses the renal involvement in various systemic diseases including diabetes and autoimmune diseases. Diabetic nephropathy is fast becoming the commonest cause of end stage renal disease all over the globe and is discussed in this book. The editors believe that this book will be a valuable addition to the reader's library.

How to reference

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