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Serum levels of sFas and sFasL in subjects with type 2 diabetes – the impact of arterial hypertension

Research Article

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Abstract: Aim. To evaluate the serum levels of sFas and sFasL in normotensive subjects with different degree of impairment of glucose tolerance as well as in type 2 diabetic patients with treated and treatment-naïve hypertension (AHT). Material and methods. 124 subjects (63 males and 61 females), of mean age 46,31±10,78 years are included in the study, divided in 5 age-matched groups: 19 subjects with type 2 diabetes (DM) and drug-controlled AHT; 30 subjects with type 2 DM and drug-naïve AHT; 30 normotensive subjects with type 2 DM; 26 normotensive subjects with prediabetes and 19 healthy controls. Serum sFas and sFasL levels are determined by highly sensitive enzyme immunoassay technique. Results. No significant differences in sFas are observed among the studied groups. The levels of sFasL are decreased in normotensive subjects with type 2 DM ($p<0,05$), while subjects with prediabetes have intermediate values. In both hypertensive groups with DM sFasL levels are further decreased. Conclusions. Serum sFas levels probably are not associated with the presence of impairment of glucose tolerance or AHT. Serum sFasL values tend to be decreased in subjects with impairment in glucose tolerance; further decrease is observed in hypertensive subjects with type 2 DM. Antihypertensive treatment does not influence the levels of sFasL.

Keywords: *sFas • sFasL • Hemodialysis • Diabetes • Prediabetes • Hypertension*

1. Introduction:

Arterial hypertension (AHT) is often associated with impairment in glucose tolerance. Hypertension is approximately twice as common in people with type 2 diabetes mellitus (DM) compared to subjects with normal glucose tolerance [1,2]. On the other hand patients with essential hypertension have greater risk of development of type 2 diabetes mellitus [3]. People with both DM and AHT have a five- to six-fold greater risk of developing end-stage renal disease compared to subjects with AHT and no evidence of DM [1]. Identification of new factors associated with the risk of AHT could be beneficial for better evaluation among type 2 diabetic patients.

The serum levels of sFas and sFasL in DM and/or AHT have been subject to previous investigations, but their potential alteration in these two diseases is still not completely clarified. The Fas/FasL system plays a key role in regulation of apoptosis of many cell types, including haemopoietic cells, tumor cells, vascular wall cells [4-6]. Serum sFas binds to FasL and sFasL, acting as an inhibitor of apoptosis; sFasL binds to Fas and sFas, acting as an inductor of apoptosis. Impairment of the Fas/FasL system in subjects with increased cardiovascular risk is reported to include increased serum sFas and decreased sFasL [7]. In subjects with type 2 DM,

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increased sFas levels are associated with peripheral vascular disease [8]. In dialysis patients, serum sFas is increased in subjects with atherosclerosis [9,10] while sFasL is not altered [10]. Serum sFas levels are elevated as well in patients with end-stage renal disease presenting with coronary artery disease [11,12].

The aim of this study is to evaluate the serum levels of sFas and sFasL in normotensive subjects with different degree of impairment of glucose tolerance (prediabetes and type 2 DM) and, additionally, to evaluate serum sFas and sFasL levels in type 2 diabetic patients with treated and treatment-naïve AHT. Thus, we could be able to estimate their potential association with impairment of glucose tolerance and/or AHT.

2. Material and methods

2.1. Subjects

One hundred and twenty-four subjects (63 males and 61 females), of mean age 46,31±10,78 years are included in this study, divided in 5 age-matched groups:19 subjects with type 2 diabetes and drug-controlled AHT (Group 1); 30 subjects with type 2 DM and drug-naïve AHT (Group 2); 30 normotensive subjects with type 2 DM (Group3); 26 normotensive subjects with prediabetes (Group 4), 19 healthy controls (Group 5). All subjects except the subjects included in Group 1 (type 2 DM and controlled AHT) are without previously diagnosed AHT and are not taking any antihypertensive drug even prescribed for other reason. All participants signed an informed consent after full explanation of the aim and design of the study.

2.2. Methods

Sixty-seven of the subjects with type 2 DM included in the study were already diagnosed at the time of their recruitment. The glucose tolerance of all other subjects with diabetes, subjects with prediabetes and subjects with normal glucose tolerance is assessed by oral glucose tolerance test with 75g glucose. Glucose tolerance is evaluated according to 2006 WHO criteria [13].

Standard anthropometric measurements – weight, height and waist circumference – are performed in all subjects.

Blood pressure is assessed by ambulatory blood pressure monitoring (Oscar 2, SunTech Medical Instruments, USA). Evaluation of blood pressure is made according to ESH 2007 Guidelines [14].

Both serum sFas and sFasL concentrations are determined by highly sensitive enzyme immunoassay techniques (Quantikine Human sFas and Human Fas Ligand immunoassay kits, manufactured by R&D Systems, Minneapolis, USA). The analytical sensitivity of sFas and sFasL assays was less than 20 pg/ml and less than 2.7 pg/ml, respectively. The intra-assay coefficients of variation (CV%) for sFas were 3.8 and 6.7 and for sFasL – 4.7 and 8.4, respectively. According to the manufacturer's values, the reference range for sFas is 4792 to 17150 pg/ml and the reference range for sFasL is 39.8 to 145 pg/ml.

Statistical analysis of the data is performed with SPSS, version 16.0. We use Oneway-Anova test to evaluate the existence of significant differences between the different groups. The correlation of sFas and sFasL with age, sex and anthropometric parameters is evaluated by Pearson correlation analysis. Accepted level of statistical significance is $p<0,05$. The data in the tables and figures are presented as mean values ± SD.

3. Results

We find similar anthropometric parameters in the different groups without any significant differences (Table 1).

Pearson correlation analysis shows significant positive correlation of sFasL with female sex ($r=0,214$; $p=0,017$) while no other correlation of serum sFas or sFasL levels with sex, age, body mass index (BMI) and waist circumference is observed among the studied patients (Table 2).

No significant differences in serum sFas were observed (Figure 1).

Table 1. Anthropometric parameters in the studied groups - Group 1 – type 2 diabetes with controlled hypertension; Group 2 – type 2 diabetes with drug-naïve hypertension; Group 3 – normotensive subjects with type 2 diabetes; Group 4 – normotensive subjects with prediabetes; Group 5 – healthy controls

Group	Number (M/F)	Age (years) ± SD	BMI (kg/m^2) ± SD	Waist circumference (cm) ± SD
Diabetes/Controlled Hypertension	19 (11/8)	48,11±7,64	31,16±4,09	105,79±9,60
Diabetes/Drug-Naïve Hypertension	30 (20/10)	47,40±11,88	29,27±4,04	100,90±10,17
Diabetes/Normotensive	30 (14/16)	47,57±8,62	27,88±4,03	96,90±13,07
Prediabetes/Normotensive	26 (8/18)	45,15±13,41	28,60±4,19	96,88±10,45
Healthy Controls	19 (10/9)	42,42±10,64	29,94±6,01	101,05±16,51

Table 2. Pearson correlations of sFas and sFasL with age, sex, anthropometric parameters

Correlations			
		sFas	sFasL
Sex	Pearson Correlation	.002	.214*
	Sig. (2-tailed)	.984	.017 *
	N	124	124
Age	Pearson Correlation	.114	-.163
	Sig. (2-tailed)	.207	.070
	N	124	124
BMI	Pearson Correlation	.115	.048
	Sig. (2-tailed)	.205	.596
	N	124	124
Waist	Pearson Correlation	.172	-.034
	Sig. (2-tailed)	.057	.708
	N	124	124

**. Correlation is significant at the 0.05 level (2-tailed).*

The levels of sFasL are decreased in normotensive subjects with type 2 DM as compared to the control group (p<0,05), and subjects with prediabetes have intermediate values between those observed in the diabetic patients and levels in the controls. In hypertensive subjects with DM – both Group 1 and Group 2 – sFasL levels are further decreased as compared to the normotensive subjects with type 2 diabetes, the difference between Group 1 (patients with DM and drug-controlled AHT) and Group 3 (normotensive patients with DM) reaching statistical significance (p<0,05). The values of Group 2 (patients with DM and drug-naïve AHT) are intermediate between Group 1 and Group 3, being closer to the values of Group 1. The most significant difference is observed between group 1 and the control group (p<0,001) (Figure 2).

4. Discussion

The anthropometric parameters show similar values among groups, with no significant differences observed. Furthermore, no correlation to serum sFas or sFasL levels was found for both BMI and waist circumference. Thus, their values would not influence the interpretation of the results.

The values of serum sFas are similar in all studied groups. As for serum sFasL, our results demonstrate that in normotensive subjects with impairment of glucose tolerance serum sFasL levels are decreased, with further decrease of sFasL in the hypertensive subjects with DM. The subjects with treated AHT have the lowest

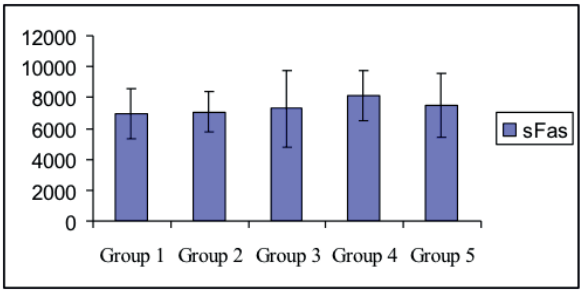

Figure 1. Serum sFas levels (pg/ml) in the different studied groups - Group 1 – type 2 diabetes with controlled hypertension; Group 2 – type 2 diabetes with drug-naïve hypertension; Group 3 – normotensive subjects with type 2 diabetes; Group 4 – normotensive subjects with prediabetes; Group 5 – healthy controls.

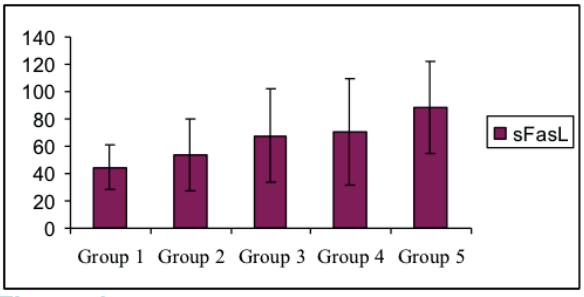

Figure 2. Figure 2. Serum sFasL levels (pg/ml) in the different studied groups - Group 1 – type 2 diabetes with controlled hypertension; Group 2 – type 2 diabetes with drug-naïve hypertension; Group 3 – normotensive subjects with type 2 diabetes; Group 4 – normotensive subjects with prediabetes; Group 5 – healthy controls.

values of sFasL, which suggests that the administration of antihypertensive treatment is not associated with normalization of sFasL values.

Cosson et al. have observed increased sFas levels in hypertensive subjects with DM [5]. Increased serum sFas is reported to be associated with the existence of newly-diagnosed DM [15]. Another study showed increased sFas values in subjects with type 2 DM, with significantly higher levels in subjects with longer duration of diabetes [16]. Protopsaltis et al. have observed positive correlation of sFas with microalbuminuria [17] and diabetic nephropathy [18-20]. Higher values of serum sFas have been found in patients in the advanced stage of renal disease as compared to the early stages [20]. A previous study in our clinical center has found no significant changes in serum sFas in subjects with DM and prediabetes [21].

Tamakoshi et al. have found a correlation of sFas only with obesity and dyslipidemia, but not with the existence of DM or AHT [22]. Another study involving women with pregnancy-induced hypertension has found no differences in sFas levels between hypertensive and control subjects [23]. Similar results have been observed in women with preeclampsia [24]. Our results, combined

with the controversial data from other authors, suggest that serum sFas levels are not associated with the existence of type 2 DM mellitus and/or AHT.

Type 2 DM is reported to be associated with decreased serum sFasL [15]. Serum sFasL levels have been observed to have negative correlation with AHT in subjects with type 2 DM [5,16]. Okura et al. have reported increased sFasL levels in subjects with AHT and atherosclerosis [25]. Decreased levels of sFasL have been observed in women with pregnancy-induced hypertension [23]. In another study, no change in sFasL levels has been found in women with preeclampsia [24]. Our results and the existing data from other authors suggest that reduced serum sFasL levels might be sensitive both for impairment of glucose tolerance and for hypertension among patients with type 2 diabetes mellitus. The antihypertensive treatment does not tend to influence sFasL levels.

Some authors report the evaluation of sFas and sFasL as part of a biomarker algorithm for coronary risk assessment already validated in two population cohorts [26]. However, our results involving serum sFas, both in this study and in the cited previous study in our clinical center, combined with the controversial data from other authors, indicate that the value of serum sFas in evaluation of other conditions associated with increased cardiovascular risk such as the existence of AHT and/or DM still remains questionable. The evaluation of sFasL levels appears to be more relevant in these cases but the value of this parameter should be confirmed by further investigation.

5. Conclusions

Serum sFas levels probably are not associated with the presence of impairment of glucose tolerance or with the presence of AHT. Serum sFasL levels tend to be decreased in subjects with impairment of glucose tolerance. Further decrease is observed in subjects with both type 2 DM and AHT. The administration of antihypertensive treatment does not appear to influence significantly the levels of sFasL.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] Nelson RG, Knowler RG, Petit DJ, Bennett PH. Kidney disease in diabetes. Diabetes in America. 2nd edn. Bethesda, MD: National Institutes of Health; 1995. Report No.95-1468. pp349-400

[2] Rachmani R, Ravid M Risk factors for nephropathy in type 2 diabetes mellitus. Compr Ther. 1999 Jun-Jul;25(6-7):366-369

[3] Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al.: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. Eur Heart J. 2007 Jan;28(1):88-136

[4] Bennett MR Apoptosis in the cardiovascular system. Heart 2002; 87(5): 480-487

[5] Cosson E, Brinquier AF, Paries J, Guillot R, Vaysse J, Attali JR, et al. Fas/Fas-Ligand pathway is impaired in patients with type 2 diabetes. Influence of hypertension and insulin resistance. Diabetes Metab 2005; 31(1): 47-54

[6] Midis GP, Shen Y, Owen-Schaub LB Elevated soluble Fas (sFas) levels in nonhematopoietic human malignancy. Cancer Res. 1996; 56(17):3870-3874

[7] Blanco-Colio LM, Martín-Ventura JL, de Teresa E, Farsang C, Gaw A, Gensini G, et al.; ACTFAST investigators. Increased soluble Fas plasma levels in subjects at high cardiovascular risk: Atorvastatin on Inflammatory Markers (AIM) study, a substudy of ACTFAST. Arterioscler Thromb Vasc Biol. 2007 Jan;27(1):168-74. Epub 2006 Oct 19

[8] García-Unzueta MT, Pesquera C, Calzada E, De la Mora A, Muñoz P, Llorca J, et al. Blood-soluble Fas levels are increased in type 2 diabetic patients with peripheral vascular disease. Horm Metab Res. 2006 Oct;38(10):673-677

[9] Masse M, Hébert MJ, Troyanov S, Vigneault N, Sirois I, Madore F. Soluble Fas is a marker of peripheral arterial occlusive disease in haemodialysis patients. Nephrol Dial Transplant. 2002 Mar;17(3):485-491

[10] Troyanov S, Hébert MJ, Masse M, Vigneault N, Sirois I, Madore F Soluble Fas: a novel predictor of atherosclerosis in dialysis patients. Am J Kidney Dis. 2003 May;41(5):1043-1051
[11] Hébert MJ, Masse M, Vigneault N, Sirois I, Troyanov S, Madore F. Soluble Fas is a marker of coronary artery disease in patients with end-stage renal disease. Am J Kidney Dis. 2001 Dec;38(6):1271-1276
[12] Tomiyama C, Higa A, Dalboni MA, Cendoroglo M, Draibe SA, Cuppari L, et al. The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. Nephrol Dial Transplant. 2006 Sep;21(9):2464-71. Epub 2006 May 30
[13] World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF consultation. Geneva; 2006
[14] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al.: The Task Force for the Management of Arterial Hypertension of the European Society for Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the management of arterial hypertension. Eur Heart J 2007; 28:1462-1536
[15] Kumar H, Mishra M, Bajpai S, Pokhria D, Arya AK, Singh RK, et al. Correlation of insulin resistance, beta cell function and insulin sensitivity with serum sFas and sFasL in newly diagnosed type 2 diabetes. Acta Diabetol. 2013 Aug;50(4):511-518
[16] Mahfouz MH, Emara IA, Omar GA Biomarkers of Oxidative DNA Damage and Soluble Fas/Fas Ligand in Type 2 Diabetic Patients. American Journal of Applied Sciences 2012; 9(4):450-458
[17] Protopsaltis T, Kokkoris S, Nikolopoulos G, Spyropoulou P, Katsaros T, Salvanos L, et al. Correlation between increased serum sFas levels and microalbuminuria in type 1 diabetic patients. Med Princ Pract 2007; 16(3): 222-225
[18] Guillot R, Brinquier AF, Porokhov B, Guillausseau PJ, Feldmann G Increased levels of soluble Fas in serum from diabetic patients with neuropathy. Diabetes Metab 2001; 27(3): 315-321
[19] Niewczas MA, Ficociello LH, Johnson AC, Walker W, Rosolowsky ET, Roshan B, et al. Serum concentrations of markers of TNFalpha and Fas-mediated pathways and renal function in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol. 2009 Jan;4(1):62-70. Epub 2008 Dec 10
[20] Baba K, Minatoguchi S, Sano H, Kagawa T, Murata I, Takemura G, et al. Involvement of apoptosis in patients with diabetic nephropathy: A study on plasma soluble Fas levels and pathological findings. Nephrology (Carlton). 2004 Apr;9(2):94-99
[21] Tankova T. Assessment of overall individual risk of diabetes. Dissertation, 2012
[22] Tamakoshi A, Suzuki K, Lin Y, Ito Y, Yagyu K, Kikuchi S, et al.; JACC Study Group. Relationship of sFas with metabolic risk factors and their clusters. Eur J Clin Invest. 2010 Jun;40(6):527-533
[23] Karthikeyan VJ, Lip GY, Baghdadi S, Lane DA, Beevers DG, Blann AD. Soluble Fas and Fas ligand in pregnancy: influence of hypertension. Angiology. 2012 Jan;63(1):35-38
[24] Bayram M, Taskaya A, Bagriacik EU, Ilhan MN, Yaman M The effect of maternal serum sFAS/sFASL system on etiopathogenesis of preeclampsia and severe preeclampsia. J Matern Fetal Neonatal Med. 2012 Aug 22. [Epub ahead of print]
[25] Okura T, Watanabe S, Jiang Y, Nakamura M, Takata Y, Yang ZH, et al. Soluble Fas ligand and atherosclerosis in hypertensive patients. J Hypertens 2002 May;20(5):895-898
[26] Cross DS, McCarty CA, Hytopoulos E, Beggs M, Nolan N, Harrington DS, et al. Coronary risk assessment among intermediate risk patients using a clinical and biomarker based algorithm developed and validated in two population cohorts. Curr Med Res Opin. 2012 Nov;28(11):1819-1830